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QUARTERLY

The seal of The Chicago Medical School is a circular emblem. It features a central caduceus (a staff with two snakes entwined and wings at the top). Surrounding the caduceus are various medical symbols, including a mortar and pestle, a book, and a pair of forceps. The words "THE CHICAGO MEDICAL SCHOOL" are inscribed around the perimeter of the seal.

THE CHICAGO MEDICAL SCHOOL
VOLUME 7, NUMBER 2
MARCH, 1946



Let your HEAD take you

(The average American today has a choice of just going where "his feet take him", or choosing wisely the course to follow. Let's skip ahead 10 years, and take a look at John Jones—and listen to him . . .)

"SOMETIMES I feel so good it almost scares me.

"This house—I wouldn't swap a shingle off its roof for any other house on earth. This little valley, with the pond down in the hollow at the back, is the spot I like best in all the world.

"And they're mine. I own 'em. Nobody can take 'em away from me.

"I've got a little money coming in, regularly. Not much—but enough. And I tell you, when you can go to bed every night with nothing on your mind except the fun you're going to have tomorrow—that's as near Heaven as man gets on this earth!

"It wasn't always so.

"Back in '46—that was right after the war and sometimes the going wasn't too easy—I needed cash. Taxes were tough,

and then Ellen got sick. Like almost everybody else, I was buying Bonds through the Payroll Plan—and I figured on cashing some of them in. But sick as she was, it was Ellen who talked me out of it.

"Don't do it, John!" she said. "Please don't! For the first time in our lives, we're really saving money. It's wonderful to know that every single payday we have *more* money put aside! John, if we can only keep up this saving, think what it can mean! Maybe someday you won't have to work. Maybe we can own a home. And oh, how good it would feel to know that we need never worry about money when we're old!"

"Well, even after she got better, I stayed away from the weekly poker game—quit dropping a little cash at the hot spots now and then—gave up some of the things a man feels he has a right to. We didn't have as much fun for a while but we paid our taxes and the doctor and—we didn't touch the Bonds.

"What's more, we kept right on putting our extra cash into U. S. Savings Bonds. And the pay-off is making the world a pretty swell place today!"

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THE CHICAGO MEDICAL SCHOOL

QUARTERLY

Published Quarterly Under the Auspices of

THE CHICAGO MEDICAL SCHOOL

VOLUME 7, NUMBER 2

MARCH 1946

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Editorials . . .

THE CLASS OF 1946

Within a few short months the Class of 1946 will be only a memory. Every class seems to be imbued with its own unique personality. Some are aggressive and audacious; others are conservative and reserved. Many mirror the ideals of their most active members; others seem to possess an underlying motivating force not attributable to any one person in the group. Though they may differ radically, on the surface, however, they all share certain basic sentiments and emotions.

There is a feeling of fear and trepidation in the heart of every graduate as he leaves the relative protection of the clinic and lecture room for the "outside world" of practical application and enforced self-sufficiency. Mistakes and lack of knowledge no longer mean just a lower grade on an examination; they may mean the difference between life and death. The graduate wonders if he possesses sufficient knowledge and ability to take a rightful place next to the tried and proven members of his profession. On his internship he makes many mistakes and errors in judgment but he soon begins to realize that he is undergoing a normal process of development. His fellow internes from other schools make the same blunders. Gradually all of them improve their ability and technique. Their mistakes become fewer in number. They are learning the art of medicine.

The *Quarterly* receives many letters from the alumni every week reflecting these sentiments. In each letter one underlying note is manifest — an expression of gratitude and affection towards the school that made it possible for them to practice medicine. They realize now that their training was adequate. They feel that they are well trained, well seasoned physicians. Someday the Class of 1946 will also have this feeling.

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A SCIENTIST'S HUMILITY

In this issue we are proud to publish an article by Sir Alexander Fleming, the discoverer of penicillin. With a humbleness amazing for so famed and honored a scientist, Dr. Fleming recounts how through the chance contamination of a staphylococcus culture, he discovered the golden drug which was later to save thousands of lives. In his article, Dr. Fleming generously and unhesitatingly shares



the credit for the later development and clinical application of penicillin with Dr. Florey and the Oxford workers. The reader will be greatly impressed by the clarity and simplicity which pervades this article and will undoubtedly want to know something more about the author.

J. D. Ratcliff, in his book *"Yellow Magic"* (Random House, 1945), describes Dr. Fleming as follows:

"Alexander Fleming is a modest man with shaggy brows and white hair. He wears stiff collars and bow ties and speaks with a quiet, deferential voice. If you were to encounter him in The Fountains or any of the other London pubs which he loves, you would certainly put him down as clerk or a shopkeeper. He was born in Lochfield near the Ayrshire village of Darvel in 1881. His father was a Scotch farmer. When he was ready to study medicine, he went to St. Mary's in London, a school, in a way, as modest as himself."

This, in brief, is a thumb-nail sketch of a great man. We wish to thank Dr. Fleming for contributing this original article to our journal. Not only will it prove of great historical interest and clinical value to the students and alumni of our school, but it will also serve as a source of inspiration to all among us who are striving to maintain the high standards and noble ideals of the science of medicine.

Editor's Note: We wish also to thank Dr. Piero P. Foa, of the Department of Physiology and Pharmacology of the Chicago Medical School for communicating with Dr. Fleming and arranging for the publication of this article.

INCIDENCE OF TUBERCULOSIS IN PERSONS OF KNOWN TUBERCULIN REACTIVITY AND ITS BEARING ON BCG VACCINATION AGAINST TUBERCULOSIS (WITH SPECIAL REFERENCE TO NURSES AND MEDICAL STUDENTS)

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IN THE COURSE of the last several years tuberculin surveys have been carried out among various groups of individuals to determine the incidence of tuberculosis infection in certain populations. It seemed that these statistics might be used for another purpose. From the time of Robert Koch's first demonstration that tuberculous animals and human beings are sensitive to tuberculin, there has been a controversy as to the relative advantages and disadvantages of this reactivity. We have attempted to cull the literature to ascertain in which individuals tuberculosis occurs more frequently; in those with an initially positive tuberculin reaction, or in those with an initially negative reaction. The statistics quoted herein deal primarily with nurses and medical students because they represent a group of individuals highly exposed to infection and to reinfection with the tubercle bacillus (1) (2).

In Table I have been listed some statistics from various hospitals and medical schools which substantiate the findings of the authors referred to above. Reports have been selected from those in Table I giving information regarding the initial tuberculin reaction of the individuals who developed tuberculosis whenever this information was available. It is important that many of these reports did not have this objective when written, but the data introduced here were culled with the idea in mind indicated above. Of the 248 cases of tuberculosis reported by authors giving figures on the tuberculin reaction, 190 occurred in initially negative reactors. This includes the 123 cases of Heimbeck (3) with which Myers (4) has taken exception because of the inclusion of erythema nodosum and pleurisy with effusion. It may be briefly pointed out that from Norway there have been numerous reports of the tuberculous nature of erythema nodosum, but it must be admitted that reports in this country indicate that there is room for doubt. In passing, it may be mentioned that Heimbeck also

included cases of these types among those individuals having an initially positive tuberculin reaction. However, if Heimbeck's cases are deleted from the table, the figures remain substantially the same; namely, 125 cases reported of which 94 occurred in initially negative reactors.

Geer (6) reported the occurrence of 6 cases of tuberculosis among 112 student nurses; 5 of these occurred in nurses having an initially negative tuberculin reaction. Amberson and Riggins (7) reported a five year study of 539 student nurses at the Bellevue Hospital in New York City. Of these, 312 were initially positive and 227 were negative to tuberculin. Eight cases of tuberculosis occurred of which 2 were in initially positive reactors, and 6 in initially negative reactors. Badger and Spink (8) reported on 275 student nurses at the Boston City Hospital. Of these, 59 per cent were positive on entrance to training, yet only one of the eight cases of tuberculosis occurring in this group was among the initially positive reactors. Marriette (12) reported on 292 nurses, both staff and student, among whom there occurred 20 cases of tuberculosis. Nine of these were in initially positive reactors and 11 in negative reactors. However, this author pointed out that only 5 of the 20 were diagnosed "adult" tuberculosis and 4 of these were among the negative reactors. Edwards (13) reported a study of 65 nurses in Nantwich, England, who had initial tuberculin reactions of 54 positive and 11 negative; yet the 2 cases of tuberculosis that occurred were among the latter group. Ferguson (14) from Saskatchewan reported on 665 nurses, both graduate and undergraduate, of whom 51 per cent were positive to tuberculin; yet of the 20 cases uncovered by periodic roentgenologic examination, only 4 were among the initially positive reactors. Scott (16), at the Winnipeg General Hospital reported the startling result that of 13 cases of tuberculosis among 274 student nurses, of whom 30.77 gave positive Mantoux tests on entrance to training,

TABLE I
INCIDENCE OF TUBERCULOSIS IN NURSES AND MEDICAL STUDENTS

Place	Number Studied	Incident of Tuberculosis		Author
		No. of Cases	Percent	
New Zealand	145(NT)*	—**	3.0	Jones (5)
Ancker Hosp.	112(NT)	6	5.5	Geer (6)
Bellevue Hosp.	539(NT)	8	1.5	Amberson & Riggins (7)
Boston City Hosp.	273(NT)	8	3.15	Badger & Spink (8)
Yale University Hosp.	191(NT)	4	2.0	Soper & Amberson (9)
Ulleval (Norway)	905(NT)	123	13.6	Heimbeck (3)
Harlem Hosp.	250(NT)	0	0	Brahdy (10)
Winnepeg General Hosp.	274(NT)	13	4.7	Scott (16)
Paris	144(NT)	6	4.1	Rist (17)
Manitoba	800(NT&S)	48	6.0	Ross (11)
Glenlake San.	292(NT&S)	20***	6.8	Mariette (12)
Nantwich (England)	65(NT&S)	2	3.1	Edwards (13)
Saskatchewan	665(N&P)	20	3.0	Ferguson (14)
Fitzsimmons Hosp.	518(NS)	8	1.5	Pollock & Forsee (15)
Harvard	484(M)	1	0.2	Fitz (18)
Hopkins	1132(M)	16	1.4	Herman (19)
Yale	427(M)	12	2.8	Soper & Amberson (9)
Women's Med. Col.	107(M)	8	7.7	Morris (20)
Stanford	420(M)	10	2.5	Barnett (21)
Wisconsin	250(M)	1	0.4	Stiehm (22)
Oslo	2568(M)	—**	5.78	Scheel (23)
Copenhagen	1577(M)	31	1.9	Holm & Helweg-Larson (24)

* Meaning of Symbols:

(NT) Nurses in Training

(NT&S) Staff and Training Nurses

(N&P) Staff and Training Nurses and Personnel

(NS) Staff Nurses

(M) Medical Students

** No figures given

*** Five cases were "adult" tuberculosis

all 13 occurred among the initially negative reactors. Rist (17) from Paris reported similar results in 144 student nurses. Here there were 6 cases among the 60 initially negative reactors and none among the 84 initially positive reactors. Mention has already been made of Heimbeck's work (3). This investigator reported a 3 to 1 preponderance of tuberculosis among initially negative student nurses in Oslo.

Among medical students, there have not been quite so many detailed studies as the above among nurses. However, Scheel (23) in Norway reported that among 361 medical students, there occurred 11 cases of tuberculosis. Of these, 9 appeared in the 57.4 per cent, who gave negative tuberculin reactions. In Copenhagen, Holm

and Helweg-Larson (24) reported that 73.6 per cent of 1,577 medical students gave an initially positive tuberculin reaction; yet of the 31 cases of tuberculosis that occurred, 19 were among the initially negative reactors.

Brahdy (10) has reported on a compilation from 5 city hospitals in New York City and pointed out several things of interest. Of the 22 student nurses whose roentgenograms showed parenchymal lesions, 17 were among initially negative reactors, 3 among positive reactors and 2 gave uncertain reactions initially. This author also pointed out that a study of 250 negro student nurses covering three and one-half years at the Harlem Hospital, revealed no cases of tuberculosis despite the fact that they were of

a highly susceptible race and moving in an atmosphere where exposure was extremely likely.

In Table II, the results are summarized in tabular form. Wherever possible an index has been recorded to emphasize the preponderance of active cases of tuberculosis among initially negative reactors. It is noted that various sources report anywhere from 3.3 to 10.3 times as much tuberculosis among the negative reactors than among initially tuberculin positive individuals (according to formula given in Table II).

This would seem to indicate that adults who have been previously exposed to tuberculosis and have developed a healed infection, as indicated by a positive tuberculin reaction, have a greater ability than do negative reactors to cope with reinfection due to repeated exposures, as probably occurs in hospital routine. Flahiff (25)

studied this problem in the Mental Hospital, Kingston, Jamaica, where all patients entering the hospital were tuberculin tested, and whether positive or not were X-rayed at regular intervals. He found that in 1,955 consecutive admissions, there occurred 131 cases of tuberculosis. These were distributed as follows: 50 cases in 1295 individuals that reacted to 0.01 mg. of O.T., or an incidence of 3.8 per cent; 42 cases in 454 individuals that reacted to 1 mg. of O.T., or an incidence of 9.4 per cent; and 39 cases in 206 individuals that did not react to tuberculin on admission, or an incidence of 18.9 per cent. The conclusion reached was that as a group, individuals who react to tuberculin are less likely to contract tuberculosis than individuals who do not react. These findings do not agree with those of the South African Committee for Medical Research (26), who showed the more sensitive natives to be more prone to contract the disease.

TABLE II
INCIDENCE OF TUBERCULOSIS IN NURSES AND MEDICAL STUDENTS AS RELATED TO TUBERCULIN REACTION

Place	Number* Studied	Initial** Tuberculin Reaction		Incidence of Tuberculosis			Index***
		No. Pos.	No. Neg.	No. of New Cases	No. Initially Positive	No. Initially Negative	
Ancker Hosp.	112(NT)	—	—	6	1	5	—
Bellevue Hosp.	539(NT)	312	227	8	2	6	4.3
Boston City Hosp.	273(NT)	162	111	8	1	7	10.3
Winnepeg General Hosp.	274(NT)	84	190	13	0	13	
Paris	144(NT)	84	60	6	0	6	
Ulleval Hosp. (Norway)	905(NT)	625	280	123	27	96	7.9
				5 adult Tb	1 adult Tb	4 adult Tb	
Glenlake San.	292(NT&S)	—	—	20	9	11	—
Nantwich (England)	65(NT&S)	54	11	2	0	2	
Saskatchewan	665(NT&S)	359	306	20	4	16	4.7
Oslo	361(M)	154	207	11	2	9	3.3.
Copenhagen	1577(M)	1161	416	31	12	19	4.4.

* For symbols see footnote to Table I.

** Tuberculin Reaction on entrance to training.

*** This figure is arrived at by establishing the following ratio:

$$\frac{\text{Number initially positive}}{\text{Number initially negative}} = \frac{\text{Number* of cases among initially positive}}{X}$$

where X = Number of cases that would be expected among the initially negative individuals. The number of cases which actually occurred in the initially negative group is divided by X and gives the number in the "index" column. For example:

$$\frac{312}{227} = \frac{2}{X} \quad X = 1.4; \quad \frac{3}{1.4} = 4.3$$

However, to this latter report several objections come to mind. In the first place, periodic roentgenograms were not taken before the onset of clinical disease, and secondly, the possibility that natives who were in the minimal stages of active disease were being included among the reactors in the statistical analysis cannot be ruled out. Also to be considered, this report deals with South African natives, who are probably more susceptible to tuberculosis naturally, and especially so when exposed to mine labor conditions with the attendant pulmonary hazards. That this is so is evidenced by the detailed post-mortem findings elaborated on in the report. It is noted that the majority of cases occurred in newly exposed individuals and ran an uninterrupted course with pathology on necropsy of extensive lymph node involvement reminiscent of primary infection type of tuberculosis (the so-called childhood type). Thus, a positive tuberculin test in these natives signified an active disease in many instances.

Of a similar nature to Flahiff's study was the one carried out by Plunkett, Weber, Siegal, and Donk (27). These authors tuberculin tested and x-rayed all the inmates of the Newark State School for Mental Defectives. They uncovered 38 cases of tuberculosis already existing, and during the course of the study, 25 new cases appeared in individuals whose tuberculin reaction was known at the time of admission. Of these, 12 occurred in negative reactors and 13 in positive reactors. However, they report that the disease was more rapid and led to 5 deaths among the initially negatives, but among the positives there were 3 deaths and the disease appeared much later. This substantiates the higher resistance of positive reactors as postulated by Flahiff. The high incidence reported in this study is not surprising, since the authors state that all the cases reported were traced to certain wards where all the open cases in the hospitals were concentrated but not isolated.

Myers (4) believes that the human body has a high natural resistance to the tubercle bacillus because so many individuals become reactive to tuberculin but so few develop clinical disease. Therefore, there must be a very marked ability to conquer the bacterium on first exposure. And he believes further that this resistance is not enhanced by the presence of a healed tuberculous process, such as the primary complex which

merely paves the way for reinfection types of the disease. As evidence, there is presented the relative mildness of the first infection form of the disease. Also, this same investigator and his co-workers (28) have shown in this study of children that there is a much higher incidence of tuberculosis in initially positive reactors than in initially negative reactors. Obviously, the former originated from a tuberculous milieu and the latter were less likely to be exposed. That studies in children are particularly difficult of interpretation is emphasized by Pope, Sartwell, and Zacks (29) who report statistical results which substantiate Myers but also indicate their awareness of fallibility due to unknown factors such as environment, exposure risks and inapparent disease at first examination. Friedman and Billings (30) have recently reported on the effects of preventorium care in 914 tuberculin positive children with and without roentgenologic findings. These authors report a relatively low incidence (1.3 per cent) of disease among their subjects which were followed for an average of 12.4 years in one group of 409 children and for 4.8 years in a more recent group of 505 children. On the other hand, Chiu, Meyers, and Stewart (28) report an incidence of 15.02 per cent in 446 tuberculin positive children followed for an average of 11.3 years. However, it is to be remarked that in the latter work, many of the tuberculin positive children with negative chest findings were not given the benefit of removal from the source of infection as is the case in children placed in a preventorium. Of necessity, a good proportion of tuberculin positive children must be in incipient stages of infection and therefore attempts to evaluate the incidence of clinical disease in reactors as compared with non-reactors must be fraught with difficulties. Further, using the reasoning that Myers employs, it may be pointed out that since so many people become tuberculin positive, but so small a percentage develop clinical tuberculosis, these individuals must possess an additional immunity conferred by the presence of a healed tuberculous process.

It should be made clear at this point that the purpose of this paper is not to present a case for hypersensitivity as opposed to immunity in tuberculosis. The evidence for and against the dissociability of these two phenomena is well

(Continued on page 30)

THE ACTION OF INSULIN ON THE METABOLISM OF PHOSPHATES

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THE intimate relationship between the metabolism of phosphates and that of carbohydrates has been known since the early work of Embden, Parnas and others on yeast, microorganisms and isolated tissues. That such a relationship exists in the intact animal is now an accepted fact, as it is known that carbohydrate undergoes a series of phosphorylation reactions during its metabolic breakdown or in the process of being transformed into glycogen. A scheme, (Figure 1), derived from a recent review by Stadie, gives the essential steps of this metabolic process, which can be divided into two parts: 1) The formation of energy rich phosphate bonds (Ph^+) from carbohydrate, and 2) The coupling of the metabolism of these energy rich compounds to physiological processes such as secretion, muscular work, etc. The phosphate necessary for the formation of carbohydrate esters seems to be derived from the inorganic phosphate of the blood, through a series of transphosphorylation reactions during which adenosinetriphosphate (ATP) and creatine phosphate (CP) are formed. Through the hydrolysis of these compounds energy is made available, such as, for instance, in the reaction $\text{Adenosinetriphosphate (ATP)} = \text{Adenosinediphosphate (ADP)} + \text{H}_2\text{PO}_4 + 11,000 \text{ calories}$. The phosphoric acid liberated is used for the formation of hexosemonophosphate, the first step in the breakdown of glucose in the body.

The role of insulin, if any, in this phosphate transport remains to be determined, but the hypothesis has been suggested that there might be a close relationship between the action of insulin upon phosphate metabolism as well as upon the metabolism of carbohydrate.

The papers about to be discussed deal with two main problems:

- 1) Whether insulin catalyzes in some way the combination of inorganic phosphate with glucose or its metabolic products or the formation of energy rich phosphate bonds such as ATP or CP, and

- 2) What is the destiny of the inorganic phos-

phate which disappears from the blood during insulin action?

The isolation and purification of insulin by Banting, Best and Collip in 1922 made it possible for many an investigator to approach these problems; but, despite a recent revival of interest in the problems of phosphorylation, this important aspect of the mechanism of action of insulin is still far from being completely clarified. In 1922 Fiske observed a decreased urinary excretion of phosphate after ingestion of sugar. This observation was confirmed by others. Sokhey and Allen found that a similar retention of phosphate follows the action of insulin and that the phosphate excretion of diabetic dogs is abnormally high. This fall of phosphate excretion is associated with a fall in the concentration of inorganic phosphate in the blood (Harrop and Benedict; Pollack, Millet, Essex, and Bollman).

Pollack and his collaborators also found that the injection of glucose does not produce a fall in the blood inorganic phosphate in the diabetic animal. This fact was made the basis of a clinical test for estimating the severity of the disease. Hartman and Bolliger found that the intravenous injection of glucose is followed by a sharp drop in the blood phosphate of the normal human subject. In diabetic patients this drop is retarded and less pronounced and does not occur at all in the more severe cases. The authors conclude their observations by stating that the demand for inorganic phosphate is apparent only when pancreatic hormone is available and carbohydrates are being utilized. Friedlander and Rosenthal reported what seems to be the reverse observation, namely that injections of sodium phosphate cause striking changes in the blood sugar of diabetic patients, but have no action on the blood sugar of normal individuals.

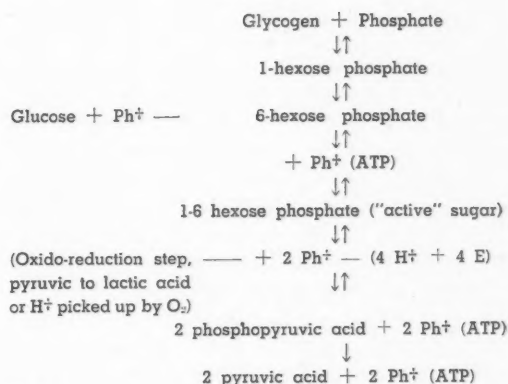
By analogy with the phenomena observed in vitro, these observations led to the general hypothesis that insulin catalyzes the formation of some organic phosphorus compounds. Several papers appeared reporting on the site of deposition of

Similarly Cori and Glotz found no change in the labile organic phosphates of the liver of mice after the administration of insulin. Contrary to these results were those obtained by Nelson, Rapaport, Guest and Mirsky. Adult rats received 2 to 5 units of insulin and, 1 hour after injection, were decapitated under deep amytal anesthesia. There was a marked and consistent increase in the total acid-soluble phosphate of the liver, mostly due to an increase in the organic fraction hydrolyzable in 8 minute's time. A simple calculation led the authors to believe that this in-

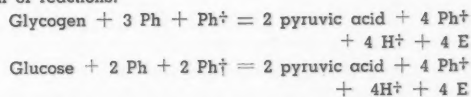
crease in liver organic phosphate could account for the main part of the decrease of inorganic phosphate in the blood plasma. It must be noted that these results, contrary to those reported by others, were obtained with excessively large amounts of insulin.

A new and different approach to the problem of phosphate metabolism was made possible by the use of radioactive sodium phosphate. Lungs-gaard perfused hind limbs of cats and added radioactive sodium phosphate to the circulating blood. He found that the addition of fructose was accompanied by the previously demonstrated drop in the concentration of inorganic phosphate and by a brisk interchange of phosphate between blood and muscle, although the actual concentration of muscle phosphate did not change. Most

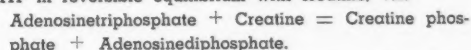
Figure 1.



Sum of reactions:



Ph⁺, which indicates energy-rich phosphate, is usually ATP in reversible equilibrium with creatine, viz:



of the radioactive phosphorus in the muscle was found in the ATP and hexosephosphate fraction. Lungsgaard did not study the action of insulin on the interchange of radioactive phosphate. This was studied by Sacks. This author used cats anesthetized with pentobarbital and injected 5 units of insulin per kg. of body weight and enough 5% glucose to avoid hypoglycemia. One half hour before the injection of insulin, the animals were given radioactive sodium phosphate subcutan-

ously. Control animals received only radioactive phosphate or radioactive phosphate and glucose, but not insulin. Four hours after the injection of phosphate the animals were sacrificed and samples of muscle tissue rapidly frozen in liquid air for phosphate analysis. Sacks found that, in the resting muscle, insulin brings about an increase in the turnover rates of phosphocreatine, ATP, fructose-6-phosphate and glucose-6-phosphate, both in the fasting and post-absorptive states. The turnover of CP and ATP was more than twice that found in the animals which had not received insulin. This was revealed by a great increase in the radioactivity of the above mentioned muscle phosphate fractions accompanied by a decrease in the radioactivity of blood inorganic phosphate. There was no significant change in the actual concentration of these organic phosphorus compounds in the muscle, but only a rise in the amount of radioactive phosphorus which they contained. According to Sacks, insulin accelerates the phosphorylation reactions which accompany the oxidation of glucose. That insulin accelerates the formation of energy rich phosphate bonds in the liver also, has been demonstrated by the work of Kaplan and Greenberg. Radioactive sodium phosphate was injected into the peritoneal cavity of fasted rats. In normal conditions the inorganic phosphate was rapidly esterified and it attained its maximum concentration in the liver 105 to 110 minutes after the injection. Most of it was found in the form of glucose-6-phosphate, ATP, adenylic acid and other esters. When 400 mg. of glucose were injected prior to the phosphate the incorporation of radioactive phosphorus into the labile groups of ATP and into glucose-6-phosphate was accelerated. Insulin injected 20 minutes after the phosphate produced an even greater acceleration of the phosphate turnover. Glucose and insulin together produced a greater effect than either alone, which is in agreement with the findings of Sacks and constitutes evidence that insulin influences the formation of energy-rich phosphate bonds. Together with a marked increase in the turnover of radioactive phosphate Kaplan and Greenberg noted also that insulin prevents the formation of liver glycogen from simultaneously administered lactate suggesting that insulin accelerates the oxidation of lactate. It was also found that the presence of malonate inhibited the increase in liver ATP brought about by insulin, suggesting

that insulin might act somewhat on the tricarboxylic acid cycle.

Further light on the mechanism of action of insulin was shown by the work of Price, Cori and Colowick. Hexokinase is an enzyme which catalyzes the reaction $\text{glucose} + \text{ATP} = \text{glucose-6-phosphate} + \text{ADP}$. This reaction is inhibited by anterior pituitary extract both in vitro and in vivo. Insulin counteracts the inhibitory action of anterior pituitary extract, although it does not enhance the hexokinase activity of untreated tissues. It is interesting to report that tissues from alloxan diabetic rats showed an inhibition of the hexokinase activity similar to that of tissues of animals treated with anterior pituitary hormone.

During a study on the action of insulin on the inorganic serum phosphate, Perlzweig, Latham, and Keefer observed the seemingly paradoxical fact that epinephrine, which has an action opposite to that of insulin on blood sugar, produces the same changes in serum inorganic phosphate as does insulin. Cori and Cori explained this phenomenon by suggesting that insulin might act through the reflex secretion of epinephrine brought about by the hypoglycemia. As pointed out by Soskin, Levine and Hechter, however, this explanation does not account for the following facts:

1. Insulin lowers the inorganic blood phosphate in the adrenalectomized dog.
2. Insulin lowers the inorganic blood phosphate even with glucose in amounts sufficient to prevent hypoglycemia.
3. The same is true when glucose and insulin are added to the blood perfusing an isolated leg.

Soskin and his collaborators studied the effect of insulin, glucose and epinephrine on normal, depancreatized and adrenalectomized dogs. Their findings can be summarized as follows. Insulin causes a decrease in the blood inorganic phosphate of all three types of experimental animals, whereas glucose and epinephrine did so only in the normal and in the adrenalectomized dog. It appears therefore that insulin is necessary for the occurrence of the phenomenon and that epinephrine is not. The fall in inorganic phosphate seems to be the result of insulin action, whether insulin is injected or its secretion is stimulated by the administration of glucose. On the other hand

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THE CONFUSION OF SEX

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Professor of Psychiatry

The Chicago Medical School

SEX has always been confusing to mankind. The constancy and degree of confusion have led to the assumption that sex and social living are not reconcilable. Many theories have been advanced to explain the "intrinsic" antagonism between sex and moral, spiritual and social integrity. For the Catholic Church it is the quintessence of sin, the "original sin", from which all mankind suffers. More recently Freud's psychoanalytic concept has found wide acceptance; he assumed that social living suppresses the "natural" drive of sex; and suppressing many of its manifestations creates a cesspool (cloaca) of anti-social impulses which disturb the social adjustment of individuals, as well as of groups, unceasingly threatening social harmony and peace.

That the confusion of sex is greater than ever before is indicated by the prevalent difficulties and failures in marital adjustment, the rising divorce rate, the widespread sexual hunger and the over-interest in sexual matters of our contemporaries, the increase in sexual delinquency and crime, and the intensified war between the sexes. A clear understanding of the causes for these conditions is missing, although a wide variety of factors is blamed. Even scientific and philosophical discussions of the problems of sex show the same confusion in regard to sex, characteristic of our era. Some denounce immorality, the lack of inhibitions, and the lowering of moral standards, while conversely others seek the solution in demanding freer expression for sexual impulses and loosening of the tight and rigid moral controls, even to opposing any concept of "sin". In all these discussions deep confusion exists in regard to the physiological, psychological and social implications of sex. A clarification of these factors seems to be essential for the understanding of the problems, such an understanding being essential for any adequate effort toward finding the solution. Only through better insight into the mechanisms of sex can we hope to find an answer to such ever disturbing and vital questions as: Why has sex been an eternal puzzle and problem for man? Why do our con-

temporaries suffer so much from it? Will a satisfactory solution of the sexual problems be possible and in which way can such a solution be found?

Let us first consider the *physiological* facts. It is amazing to note that *very* few scientists, to say nothing of the lay public, understand the significance of these facts which are well described and well understood in their physiological mechanisms. We know the glandular nature of the sexual urge; we understand the physiological mechanisms and manifestations of sexual excitement; we have scientific approaches to the problem of sexual gratification—but we fail to recognize the essential nature of human sex. Public opinion regards human sex as identical in structure with animal sex, an opinion not at all true and contrary to facts. It is generally accepted that the animal kingdom is dominated by two fundamental "natural urges", which serve for the maintenance of the individual and of the species. Hunger is the stimulation to seek food in order to preserve the individual existence; and sex impels each being to act in the service of maintaining his species. Are human beings, as members of the animal kingdom, equally compelled by these two drives? Most people would answer "yes". And there they would make their fundamental mistake.

These original natural urges are modified in human beings to such an extent that they have completely lost their original function and meaning. As man learned to form strong social affiliations in order to overcome the power and the influence, the danger and threat of nature around him, so he learned equally to master nature within himself. He is no longer exposed to and dependent upon the elements around him, but rather controls them in increasing degree to the point where at present he is discovering the deepest secret of nature, that of nuclear energy and putting it into his service, be it for destruction or benefit. Throughout the many thousand years of social living, when the needs of social communication and integration became the preva-

lent motive for all his actions, man has learned to gain complete power over the natural forces *within* himself, over hunger and sex. But unfortunately he is still not aware of this power which he exercises constantly. And there are good reasons why we refuse to admit to ourselves our control over our desires. But let us first examine in which way man differs from other things in regard to sex.

With the exception of very few beings who, incidentally live in closest social organizations, like bees and apes and domesticated pet animals, all beings depend in their sexual activities entirely upon the physiological activity of their glands. The glandular activity compels sexual activity, and the lack of physiological readiness prohibits it. The animal can copulate only when the female is in heat; but the presence of a ready male of the same species is compulsory for action, which can only be prevented then through brutal force by either a rival or other outside power. These two characteristic elements of *limitation* and *compulsion* are certainly not applicable to human beings. Man can experience sexual desires and satisfy them *at any time*, without any consideration for the feminine menstrual cycle, even in the period of life when the sexual glands are not yet developed (i.e., before puberty), and after they have ceased to function, (as after climacteric and even after castration). Castrated animals are sexless; human beings do not lose their sexual desires and their ability to copulate, if castrated after puberty, after adult sexual patterns have been developed and trained. This freedom of action is also revealed in the variety of sexual objects available to man for sexual gratification. Sex can be directed at a member of the opposite sex (heterosexuality), at a member of the same sex (homosexuality), at the person himself (autosexuality), at an animal (zoerasty), a dead (necrophilia) or an inanimate object (fetishism). There is no physiological limitation and restriction for any individual to choose the object he desires and to derive gratification from it.

Human sex is polymorphous.

On the other hand, sex is no longer compulsory for man. If he chooses he can refrain from any sexual activity, irrespective of his own glandular functions and of opportunities offered to him. He can suppress his sexual interests and desires, even though he might not be aware that he himself is doing it. Subjectively man still may feel

a compulsion or an inhibition; but these experiences are not based on *physiological* mechanisms but are merely of a *psychological* nature. For human activity is entirely controlled by psychological mechanisms. The physiological functions of sex are completely at man's service. He may use them or neglect them as he pleases and chooses.

This brings us to the second point which needs clarification: *the psychological aspect of sex*. All sexual experiences of human beings are produced, colored and directed by psychological motivations. It is up to each individual to become stimulated, how and to what to respond, how long to remain interested, to what extent to commit himself, to develop superficial or deep emotions. The physiological mechanism of sex is supplemented by corresponding emotions which are called Love. There are as many types of love as there are lovers and each person can experience a great variety of the emotions of love. Love is the expression of wanting and desiring, regardless of how constant or superficial the desire may be.

The type of love, of which a person is capable, the incident of falling in love and of falling out of love, persistency or fickleness, all depend upon the whole personality and on the goals which a person sets for himself, often without being aware of them. We can use love for good or for bad, for heaven or hell, as virtue or sin, for social participation or isolation. Everybody seeks love and happiness obtainable through it. But only a courageous person with social interest is capable of "true love"; this term indicates merely a type of love which is constructive, constant, deep, uncompromising and directed toward a suitable partner. However, as many of our contemporaries are discouraged, socially maladjusted, on the defensive, and unwilling to give themselves completely, the fulfillment of love becomes in our time an exception rather than the rule. Many either entirely avoid falling in love, or choose the wrong partner, or they may abuse the human capacity for sex and love in some other way, which either does not lead to matrimony at all or disturbs marital adjustment and happiness.

Faulty attitudes and concepts of sex and love originate in childhood. The experiences of a child who observes father and mother as the first and most impressive representatives of both sexes, the ideas about masculinity and femininity, the

impressions of sex and its possible dangers very frequently disturb the attitude of the child toward sex and affect his future sexual life. His future experiences depend largely upon his belief or disbelief in the possibilities of men and women living peacefully together as demonstrated by the parents. Fundamental outlooks in regard to the opposite sex are established through the personal experiences which a child has with parent or sibling belonging to the opposite sex. Such experiences promote or diminish the willingness and capacity to cooperate, to trust, and consequently, to love. Much depends also on the willingness of the child to accept his own sexual role and on his understanding of what the specific masculine or feminine role implies. Girls especially are often impressed with the dangers and humiliation, hardships and impositions, which can be experienced through sex. Sex may appear as ugly, cruel, ignominious and shameful. All depends upon the child's proper education in regard to sex.

The sexual behavior, however, is only one aspect of social participation in general, as love, sex and marriage constitute only one of the three life tasks, the other two being work and social intercourse. The use which a person makes of sex and love is in line with his approaches to life in general, with his abilities to get along with other people, with his inclination to play the social game or to evade social obligations. Sex can be used either as a tool of mere pleasure, or as an opportunity to give oneself to another person. The fulfillment of sex does not permit distance; therefore, the nature of sex relationships depends upon the general ability of a person to come close to others. Persons who always keep aloof, who are constantly on the defensive, and who have trained themselves to be distant, cannot behave differently in love and sex. In such cases it becomes difficult to admit to one's own conscience the purpose and methods for which one uses—or better, abuses—sex and love. The need to excuse antisocial attitudes, and unwillingness to participate and to fulfill the social responsibility to marry and to cooperate with one's spouse, prevent the recognition of one's own complete control of sex and love. Such recognition would imply full responsibility for one's actions; in order to avoid the responsibility one prefers the assumption of being the helpless victim of sexual drives and emotions, which may

come or go without conscious volition, as almost mystical and unpredictable elementary forces. In that way love and sex may function like neurotic symptoms which also serve as excuses for uncooperative behavior while permitting the belief in one's own good intentions.

Human sex can serve in three ways. Originally, it was mainly an instrument of procreation. As the knowledge of birth control and planned parenthood increased, people became independent of the procreative function of sex, despite all religious and legal proscriptions. Freed from such traditional concepts, people learned to regard sex primarily as a tool of pleasure, which appears to self-indulgent persons as the only sense of living. Sex can, however, serve another function: as an agent to unite two people most intimately and completely into one spiritual and physical unit. Monogamy appears in this light as the most adequate form for the fulfillment of the deepest needs for love and belonging. It seems that our contemporaries are very ill equipped for close human relationships. Our generation suffers from a lack of social interest which disturbs all personal interrelationships and equally the relationships of groups. Therefore, the problems of sex are closely related to the social problems confronting our time.

This brings us to the *social aspect of sex*. Sexual behavior has been recognized in its dependency upon social pattern and custom. The moral concepts regulating sexual activities are always in line with the social conventions governing the behavior of all members of a group. For this reason we must regard the social behaviour of our contemporaries as an expression of the social forces dominating our present society and culture. The chaos and confusion in regard to sex correspond to similar confusions in other fields of human relationships. They are part and parcel of the confusion in political developments, economic struggles, religious and racial antagonisms, moral and social uncertainties, characteristic of the distorted human relationships of our times. The war between the sexes is only one aspect of a general social condition which makes man the enemy of his fellow-man. However, the antagonism between men and women affects the most intimate relationships of family life, and therefore disturbs the personal lives perhaps more than any other conflict of our time.

To be sure, the war between the sexes did not

arise only recently. It existed in all past history, although perhaps never as overtly as today. This deep antagonism between men and women is entirely of a social nature; as it affected the sexual lives throughout history, it made love and sex an unsolvable social problem. Despite men's experiences of sex throughout many hundreds of years, despite the control which man gained over the physiological forces of sex, he has not yet learned to adequately control and organize the relationships between the two sexes. Until very recently we did not recognize that there ever was anything wrong in the relationship between men and women, and much less did we know what was wrong. It took all the years of human social living to come to the point on which we stand today in our culture. Today we become aware that harmonious human relationships are possible only on the basis of *full social equality*. Conflicts, competition and warfare are inevitable, as long as such fundamental equality is not established.

The idea of equality is not new. Although equality does not exist in the animal kingdom, man discovered this concept several thousands of years ago, shortly after our present civilization began. The Greeks labored with the idea of "Democracy" in which all people, participating in the rule of their group, should have full equality as sovereigns, as rulers. The Greek Stoics were the first to formulate a concrete concept of human equality; the late Roman lawyers then took it up. But the ancient world was unable to establish human equality because its culture was based on a slave economy which prohibited any establishment of true human equality. Before the ancient culture collapsed, due to its inability to progress, it created a spiritual manifestation of a fundamental human equality, namely Christianity. The early Christians recognized the equality of man before God, although such concepts were given up by the Catholic hierarchy during the Medieval World in accordance with the then existing social and economic conditions. The last few centuries saw a strong renaissance of democratic ideas. The French and the Russian Revolutions ending feudalism, the Bill of Rights and, more recently, the Atlantic Charter, and the Declaration of the Four Freedoms are milestones in the present struggle to establish real democracy. We are in the midst of this struggle but already at the point where we can visualize the final solution.

This general tendency toward human equality affects the relationships between men and women in a peculiar way. We must keep in mind that nowhere in history has equality between men and women been found, although it was not always the man who dominated as he does in the cultures with which we are familiar, including our own. We have reports of societies which were ruled by women (matriarchate), where women possessed political, social, economic and sexual privileges and rights which are considered typically masculine in our culture. The rights of women changed, decreased or even got lost in a new patriarchal setup, but never was there any intermediate stage of equality, as the concept of equality was unimaginable to these cultures. A slight tendency toward equality between the sexes occurred in the Greek and Roman cultures when they moved toward a democratic organization of society. Some of our typical present-day sexual and marital problems occurred during such cultural epochs, as the spread of homosexuality in Greece. Then feminine equality threatened to become a reality but was diverted by men into equality, limited to a few members of the feminine sex (hetairae), who were permitted to associate with men on an equal basis. Increased strain in the relationship between the two sexes indicate that growing equality does not reduce the tension and the conflicts between men and women; on the contrary, it increases them. This fact is of utmost significance. It not only explains many peculiar difficulties and conflicts in the sexual and marital relationships of our time; it illuminates the significance of other social and cultural conflicts which our contemporaries have to face. Analyzing and evaluating the effects which growing equality has in the relationships between men and women may help us to understand the implications of growing equality between other groups and classes of people.

The emancipation of women occurred as a by-product of liberalism and capitalism, developing since the collapse of feudalism. As other previously underprivileged groups strove for political and social rights, so did women. Increased competition resulted from the new freedom for all individuals and groups to gain social and economic position and power. A characteristic situation arose: The previously latent and dormant antagonisms were permitted to come into the

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CARCINOMA OF THE RECTUM

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EARLY diagnosis of carcinoma of the rectum is the responsibility of the physician who is in general practice.

It is the family physician who usually first detects carcinoma of the rectum; that is, if he makes it a point to eliminate or confirm the possibility of cancer in disturbances of the rectum.

ETIOLOGY:

Incidence: About 15% of all carcinomas occur in the large intestine. Hendrick recorded 4,298 cases of carcinoma of the colon classifying them according to location: Cecum, 15%; transverse colon, 16%; sigmoid, 13%; rectum and recto-sigmoid, 56%. Anal carcinoma (squamous) accounts for less than 1% of the disease.

Age and Sex Incidence: In our series of cases of carcinoma of the rectum 55% occurred in men, and 45% in women. The average age of occurrence was 55 years; 90% were more than 40 years of age, and 10% were less than 40 years; 2% were less than thirty years of age.

It is evident therefore, that in any patient over forty years of age who presents a history of bleeding, malignancy of the rectum should be considered.

A history of bleeding, at any age, however, should suggest the possibility of carcinoma, and the necessity for appropriate examination.

Many of these cases in our clinic had had previous treatment of some kind. Many of them had had hemorrhoidectomies, fissurectomies, fistulectomies. Perhaps because the physician did not use the sigmoidoscope, the lesion higher up was neglected; or perhaps the higher lesion occurred since surgery was done. In most of these cases the presence of advanced carcinoma suggests that the early lesion was overlooked.

Chronic irritations which may be chemical, mechanical, or infectious, are predisposing factors of malignancy in the rectum. Cancer has been found in areas in which there was a high degree of acidity, such as the stomach, the cervix, the urinary bladder, and the mouth.

It is interesting that the small bowel, which is

alkaline, shows about one-tenth of all malignancies.

Heredity is a questionable factor.

Pre-cancerous lesions are important. In this connection polyps (the so-called adenomatous polyps), should be emphasized. These are frequently forerunners of malignancy in the rectum. If on routine examination, regardless of size or type, an adenomatous polyp is found, it should be removed. Failure to do this is likely to result in malignancy in later life.

TYPE AND CHARACTERISTICS OF LESION:

Type: Of these neoplasms, 95% were adenocarcinomas, 3% epitheliomas, 1% colloid carcinoma, and 1% lympho-sarcoma.

Size: A lesion of 3 cm. or less was considered small, up to 6 cm. moderate, and more than 6 cm. was considered a large growth.

Mobility: In a third of the cases the lesion was mobile, another third fairly fixed, or somewhat mobile, and in another third was entirely fixed.

SYMPTOMS:

Any change in bowel habit, especially early-morning diarrhea and bleeding, suggests cancer and calls for sigmoidoscopy and roentgenologic study. Diarrhea which wakens the patient at night is often the result of organic disease. Most patients have indefinite symptoms for a year or more.

In the right side of the colon there is a dyspeptic syndrome in which there may appear discomfort and tenderness in the epigastrium or the right side of the abdomen with nausea, eructations, a feeling of fullness after meals, and distention of the lower abdomen. A palpable mass may be the first evidence of cancer of the cecum or ascending colon; it may be concealed by fat.

On the left side obstruction occurs six times more frequently than on the right. Here the familiar manifestations are constipation and bright red or dark red blood mixed with feces or mucous. Acute obstruction is rare. More often partial and progressive obstruction occurs. There is vague malaise, dehydration, intoxication, con-

stipation, visible peristalsis, and loud borborygmus. Weakness and dehydration often concern the patient more than the other symptoms. Real diarrhea is uncommon; the stools may be numerous, but often consist of mucous. Pain is not a predominant symptom. Colic due to obstruction and gaseous distention may occur.

In the rectum and recto-sigmoid, carcinoma may cause early symptoms, many of which are common to other disorders. Bright red blood, mixed with or streaking the stool, is frequently observed, but not often as an early sign. Constipation, often without distention, usually increases in severity and sometimes alternates with diarrhea; it is usually neglected until tenesmus and pain develop. There may be a heavy sensation which is not relieved at stool.

PAIN:

The mucous membrane of the rectum has no sensory nerves and is insensitive to pain. In early malignancy there is no pain. When there is pain in the rectum, the carcinoma has invaded nearby structures in the pelvic region. The pain is excruciating. The pain may be in the rectum, the abdomen, or the bladder. It is peculiar that the patient does not know where the pain is. The patient may have the sensation of having to urinate frequently, or he may not be able to differentiate between the sensations to urinate or to defecate. He may on urination, actually discharge from the rectum as well.

Pain in the abdomen may occur because the bowel above the neoplasm becomes distended and affected, so that abdominal discomfort results.

In 83% of our cases, the pain produced by the rectal cancer was in the abdomen. That is important. The patient may say he has pain in the abdomen, although he has a cancer of the rectum. In 40% of the cases the pain was in the back or hip, and in 41% of the cases it was high up in the rectum, in which case the patient may have spoken of 'pain up inside somewhere.'

In 65% of the cases pain was constant; in 45% there was high rectal pain, and in 15% low rectal or anal pain, and in 2% there was so-called indefinite pain.

Constipation: Patients report a feeling of incomplete elimination of the bowels. Usually they are not certain whether this form of stasis is constipation.

Diarrhea is another symptom which becomes sufficiently troublesome and alarming to the patient to induce him to consult a physician.

Discharges: Discharges and especially mucous mixed with blood is a frequent symptom and one to which the physician should be alert.

Lesions: Fissures and hemorrhoids are the most common presenting symptoms. Proctoscopic examinations in thirty-five per cent of our cases revealed that the location of the neoplasm was either low rectal or anal; that is, including the anus and the lower half of the rectum. In 60% it was high rectal (the upper half of the rectum), and in only 5% was it recto-sigmoidal or sigmoidal. There was some degree of interference with the passage of the feces and many patients did complain of obstruction, but that was not the chief complaint.

DIAGNOSIS:

Seventy-five per cent of the cancers of the rectum are in such position that they may be recognized with the use of a proctoscope; therefore it is imperative to use the proctoscope early.

A method of examination for diagnosis is herewith suggested:

1. Examine the external anus to see whether there is any protrusion, whether there are fissures, hemorrhoids, or any other pathologic condition.
2. A digital examination is done to determine whether a neoplasm is present. If a growth is present, determine its position, so as to know where to proceed with the proctoscope. Also, determine its degree of mobility. The digital examination will likewise reveal the presence of any polyps, or papillae, and it will also disclose disorder of the prostate. One should note the size and consistency of the prostate. In women, the cervix of the uterus is similarly examined. The coccyx should not be overlooked during digital examination.
3. Anoscopic examination is done to determine whether there are any neoplasms low down in the anus, or within the visibility range of the small anoscope. The presence of fissures or internal sinuses or blind sinuses and the degree or size of any hemorrhoids will thus be disclosed.
4. The patient is placed on a three day meat-free diet following which he submits a stool for

examination. If occult blood is present, carcinoma of the rectum or colon must be ruled out or confirmed in diagnosis.

5. Then, a sigmoidoscopic examination is done. The patient is prepared properly for examination by taking several enemas. The search should be made as high as ten to fifteen inches up in the rectum and sigmoid to determine the possibility of any polyps, which are the forerunners of carcinoma. A polyp, to be sure, may be degenerated without being malignant at the time of examination. In using the sigmoidoscope, be careful not to introduce it with the obturator too far, because of the possibility of producing severe hemorrhages if there is cancer of the rectum.

Pass it just beyond the sphincter; remove the obturator, and pass the scope under vision. Do not subject the patient to too much discomfort.

6. If the sigmoidoscopic examination is negative, and there is occult blood present, a complete roentgenologic examination should be made.

TREATMENT:

Radiotherapy: I am in favor of using X-Ray or radium, but I believe that radiation should be used in cases of malignancy only in order to reduce the tumor mass somewhat, and to localize the infection surrounding the carcinoma. Later, the surgical procedure should follow.

Fulguration: I have used fulguration in a number of selected cases. Fulguration is burning. It is the same as using an actual cautery. A spark is produced, and one can actually see the spark burning the tissue. In employing fulguration, the position of the cancer is important. It should not be used if the malignancy is in the anterior quadrant, because there will be penetration and probable injury to the prostate or the bladder. Fulguration should not be used when the malignancy is near a viscus for the same reason. When the malignancy is on the posterior quadrant, fulguration will give excellent results.

If the carcinoma is above the peritoneal reflection do not use fulguration. Only from five to ten per cent of the cases of carcinoma are amenable to this treatment because of their location.

Surgery: Surgical resection is indicated whenever possible. The selection and performance of the best operative procedure for each individual

patient requires training and experience with colonic surgery. Good pre-operative preparation of the patient increases the number of operable cases, and thereby the number of potentially curable cases. Preoperative hospitalization is necessary for at least one week.

Provide a low residue diet of 2000 to 3000 calories daily, composed of carbohydrates and low residue proteins, such as eggs, bacon, very concentrated beef or chicken soup, and beefsteak (chewed but fiber not swallowed).

Give blood transfusions for even mild degrees of anemia. Correct dehydration by oral fluids if possible; otherwise give 5% dextrose and/or physiological saline intravenously.

Sulphasuxadine, sulphaguanadine, or sulphathaladine in large doses for 1 week makes for a clean field.

PROGNOSIS: Carcinoma of the ano-rectum spreads slowly and if operated upon early offers a good percentage of five-year cures. Metastasis does not contraindicate surgery. Life and comfort have been prolonged by surgery, radium, X-ray and surgical diathermy even in the presence of fixation and metastasis.

The majority of recurrences occur within two years. The younger the person, the more malignant is the lesion and the more likely the recurrence; the older the person the less malignant the lesion and the less likely the recurrence. The more selective the cases the greater are the number of five-year cures.

* * * * *

Swellings appeared about the ears, in many on either side, and in the greatest number on both sides, being unaccompanied by fever so as not to confine the patient to bed; in all cases they disappeared without giving trouble, neither did any of them come to suppuration, as is common in swellings from other causes . . . They seized children, adults, and mostly those who were engaged in the exercises of the palestra and gymnasium, but seldom attacked women. Many had dry coughs without expectoration, and accompanied with hoarseness of voice. In some instances earlier, and in others later, inflammations with pain seized sometimes one of the testicles, and sometimes both; some of these cases were accompanied with fever and some were not; the greater part of these were attended with much suffering.—Hippocrates, on Parotitis.

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Section II Aphorism 2

When sleep puts an end to delirium, it is a good symptom.

Alumni News

It is with great sorrow that we report the passing of Assistant Surgeon (R) Arthur L. Loebel (CMS '43). Dr. Loebel's untimely death came while in the service of his country with the United States Coast Guard. After completing his internship at the Beth Moses Hospital of New York, he received the degree of Doctor of Medicine and entered the service. Dr. Loebel is survived by his wife and young baby daughter who are residing at 1690 President St., Brooklyn, N. Y. We of the *Quarterly* feel sure that we express the feelings of all those who knew him at school, during his internship, and in the service when we say that we were deeply shocked to learn of his sudden demise. We extend to his wife and family our most sincere sympathy.

1935—Dr. Reuben Marbell has resumed his practice of medicine after service overseas, and is now located at 5058 S. Ashland Ave., Chicago.

Thanks to Dr. J. R. Chalfin for a very welcome letter. Dr. Chalfin is now practicing in Venice, Illinois. Among other things far too numerous to mention, Dr. Chalfin is District Surgeon of the Wabash Railway Co. & Ann Arbor Rd., Secretary of the hospital staff of St. Elizabeth's Hospital of Granite City, Ill., and a member of the Executive Committee of the same hospital.

1937—Dr. Anthony G. Cesare, recently discharged from the Medical Corps, A.U.S., where as a Major he was in charge of surgery for the 55th Field Hospital, was a very welcome visitor. Dr. Cesare has now returned to his medical practice and is located at 9113 Commercial Ave.

Another former Major of the Medical Corps, A.U.S., Dr. Samuel C. Noto, has returned home and resumed his medical practice at 1145 Berwyn Ave., Chicago.

1938—In spite of a fire which was rapidly consuming the United Mine Workers Hospital of West Frankfort, Illinois, Dr. Albert Norman continued to work frantically against time to deliver a young

baby boy. The new mother was totally unaware of what was going on, and only after being safely removed from the burning building was she informed of her narrow escape and of Dr. Albert's fortitude.

Dr. Lewis Tanenbaum has been discharged from the Army Medical Corps, and has resumed his practice in his former location, 9 S. Kedzie Ave., Chicago.

Dr. Hannibal Paolozzi was recently discharged from the Medical Corps of the A.U.S., and has opened his office at 1809 W. 47th St., Chicago, Ill.

Another very welcome visitor to the school was Dr. Herman H. Hill. Dr. Hill is now on terminal leave after serving in the China-Burma-India theater and soon plans to resume his practice.

1939—Drs. Sam Cooper and Morris Fox recently came to see us at school. Both doctors have been discharged from the service, and will resume their practices once again. Dr. Fox will open his practice at 4010 W. Madison St.

1940—The other day, Drs. E. J. Levine and Harry J. Barnett felt the urge to gaze upon the "old alma mater" after their recent discharge from the service. We were happy to see them. They will soon be returning to their former practices.

Major Gene Arenson is now on terminal leave, and is rapidly getting back into the swing of things. He is Associate Medical Director at the Danish-American Hospital.

Capt. Louis Berlin writes us from Percy Jones General Hospital, Battle Creek, Michigan, that he will soon receive his discharge after which time he expects to go on with graduate study in neuropathology and neurology.

1942—Captain Howard Sloan stopped in to say hello a short time back. Capt. Sloan is eagerly awaiting his discharge from the Army, after which time he expects to take a residency in medicine.

1943—Drs. Anthony Bolino and Frank I. Uyeno have recently opened new offices here in Chicago. Dr. Bolino is located at 550 W. North Ave., and Dr. Uyeno at 841 E. 63rd St.

1944—Dr. Milton Wohl announces the opening of his new office at 2700 W. North Ave., Chicago. Dr. Wohl has also been recently appointed to take charge of the Student Health Office at School.

Dr. Milton Plafker tells us he is doing a lot of work in the field of urology lately. His new office is at 639 W. Diversey Parkway, Chicago.

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In answer to recent inquiries we should like to report that Joseph G. Berkley, who left school at the start of the war for the Army Air Corps, is now owner, publisher, and editor of the Dodge City Journal, Dodge City, Kansas. Also Marshall Persky and Hy Kaplan have been discharged from the armed forces and are now back at school.

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To all of our graduates who have just recently opened their offices, may we extend our best wishes for a very successful practice. To those of you from whom we have not heard as yet, "What's holding you up?" We at school and your former classmates who receive each issue of the *Quarterly* would like to know what you are doing. So take a few moments off from that busy practice of yours and drop us a line. How about it?

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ALUMNI RECENTLY SEPARATED FROM SERVICE

Clark, Cliff L.	CMS 1937
Hybke, Zenon S.	CMS 1935
Zaborsky, Emil R.	CMS 1938
Lawler, Frank C.	CMS 1939
Frutchey, Lloyd	CMS 1935
Noto, Samuel C.	CMS 1937
Willett, Bradford J.	CMS 1933
Arenson, Gene J.	CMS 1940
Hill, Herman H.	CMS 1938
Marbell, Reuben	CMS 1935
Sheade, Martin	CMS 1939
Weissman, Louis	CMS 1939
Fisher, George E.	CMS 1938

Fernando De Leon	CMS 1929
Lawrence B. Kalom	CMS 1940
William J. Kroulik	CMS 1937
Carl H. Resnick	CMS 1934
Henry M. Terone	CMS 1938
Aaron S. Cahan	CMS 1939
Gervaise P. Pallasch	CMS 1939
Adio A. Freedman	CMS 1940
Hilbert A. Jabczynski	CMS 1933
Ladislau J. Jurek	CMS 1934
Stanley C. Kucharski	CMS 1934
Caryl C. McIntyre	CMS 1936
Eugene J. Sodaro	CMS 1937
Allen R. Morrison	CMS 1933
Morris Peterson	CMS 1938
Bernard Schwartz	CMS 1935
Herbert Tashman	CMS 1938
Charles L. Watters	CMS 1936
John Jacob	CMS 1938
Baranov, Lester J.	CMS 1938
Barnard, Robert D.	CMS 1932
Barnett, Harry J.	CMS 1940
Bartlett, Isaac E.	CMS 1939
Bonick, Thomas J.	CMS 1939
Burckart, Glenn A.	CMS 1930
Cermak, Miles	CMS 1940
Cohen, Bernard L.	CMS 1936
Comarr, Avron E.	CMS 1940
Cooper, Samuel S.	CMS 1939
Ciulini, Fausto	CMS 1937
Errico, Silvio	CMS 1936
Feldser, A. Vernon	CMS 1937
Fox, Morris	CMS 1939
Friefeld, Nathan	CMS 1941
Gannon, Paul A.	CMS 1934
Geller, Joseph	CMS 1941
Graf, Carl N.	CMS 1939
Green, Martin W.	CMS 1940
Green, W. W.	CMS 1940
Grizzaffi, Anthony L.	CMS 1938
Hamilton, George R.	CMS 1937
Hubner, Charles F.	CMS 1934
Kadas, Louis	CMS 1935
Karay, George	CMS 1935
Lando, Leon	CMS 1936
Levine, Edward J.	CMS 1940

(Continued on page 34)

THE DEVELOPMENT AND USE OF PENICILLIN

Sir Alexander Fleming, F.R.C.P., F.R.C.S., F.R.S.

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I HAVE often been asked why I named a substance "Penicillin." The reason is very simple—an active substance was made by a mould of the genus *Penicillium* (an old botanical name) so it was simply following orthodox practice to name this substance Penicillin. There are many precedents in pharmacology, for example, digitalin from digitalis, aloin from aloes, etc.

Let us for a moment trace the life history of a penicillium. It commences from a microscopic

we are only concerned with one group — the chrysogenum, notatum group.

The colony of a penicillium is familiar to all of us—we can see it on jam, cheese, or other household articles. It may attain a large size and a large colony will bud off myriads of spores, many of which float around in the air. If all these spores developed it would be a misfortune and this world would be very mouldy, but fortunately, most of them do not reach surroundings

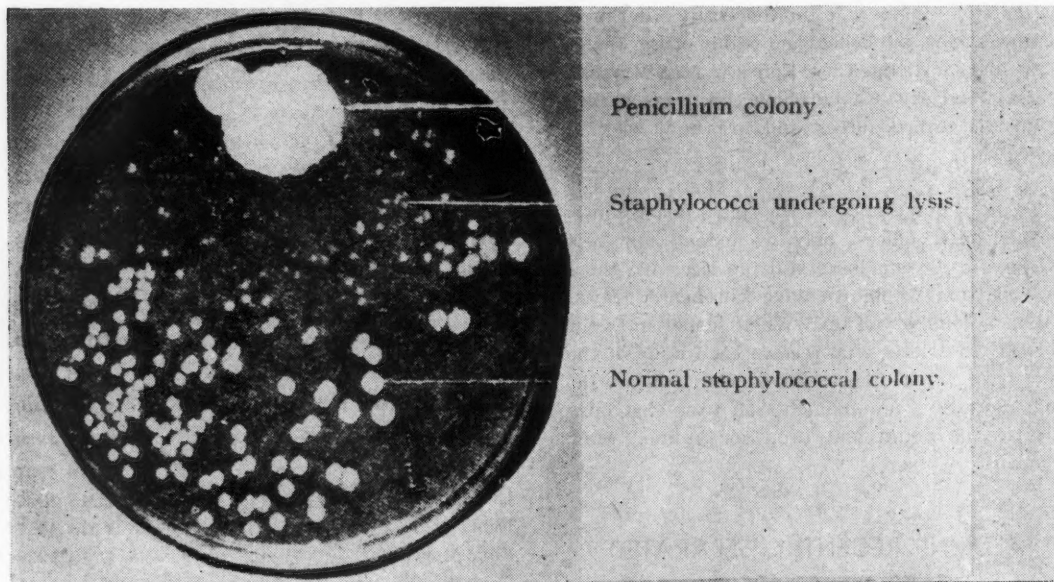


Figure 1

Photograph of a culture plate showing the dissolution of Staphylococcal colonies in the neighborhood of a penicillium colony.

spore. When this is deposited in surroundings congenial to its growth it germinates and grows out into a tangled mass of hyphae. Soon, however, as it grows it sends into the air special reproductive hyphae which branch in a peculiar manner and which bud off spores from their terminal branches. The whole reproductive hypha somewhat resembles a brush hence the name penicillium. There are hundreds of different

species of penicillia but in regard to penicillin congenial to their germination.

In 1928 I was engaged in a study of staphylococcal variation and this necessitated the removal of the lid of the culture plate at intervals. This, of course, risked contamination of the culture from the air and sure enough one of the plates was contaminated by a penicillium spore which grew out into a colony. This contamination of a

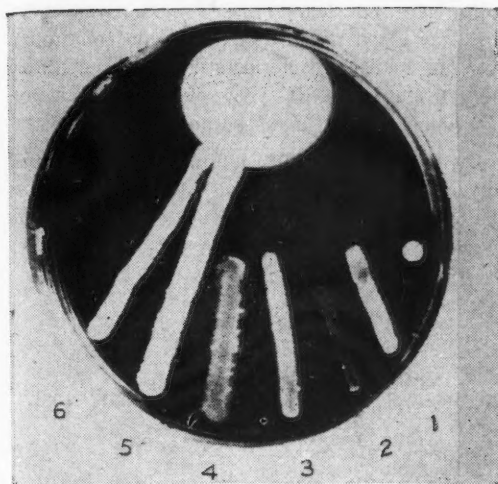


Figure 2

Different bacteria streaked radially to a 4-day-old colony of *P. notatum* on agar.

- | | |
|-----------------------------|------------------------|
| 1. <i>Staphylococcus</i> | 4. <i>B. anthracis</i> |
| 2. Haemolytic streptococcus | 5. <i>B. typhosus</i> |
| 3. <i>B. diphtheriae</i> | 6. <i>B. coli</i> |

culture plate with moulds is not unusual—all bacteriologists have encountered it many times but in this particular plate the mould had induced a most remarkable change—all the staphylococcal colonies around the mould were undergoing lysis. (Fig. 1). This was to me an unprecedented appearance and seemed to call for investigation.

The first thing to do was to obtain a pure culture of the mould and this presented no difficulty using the ordinary bacteriological methods. It was found that the mould would not grow at 37°C but grew well at room temperature. Then some of the spores were planted in a spot towards the periphery of an ordinary culture plate. They were allowed to grow at room temperature for 4 or 5 days when the colony had reached a size of between 1 and 2 centimetres. Then different microbes were streaked across from the edge of the plate to the mould colony and the culture was incubated overnight at 37°C. Next day it was found that while some of the microbes grew right up to the mould others were inhibited for a distance of two centimetres or more. (Fig. 2.)

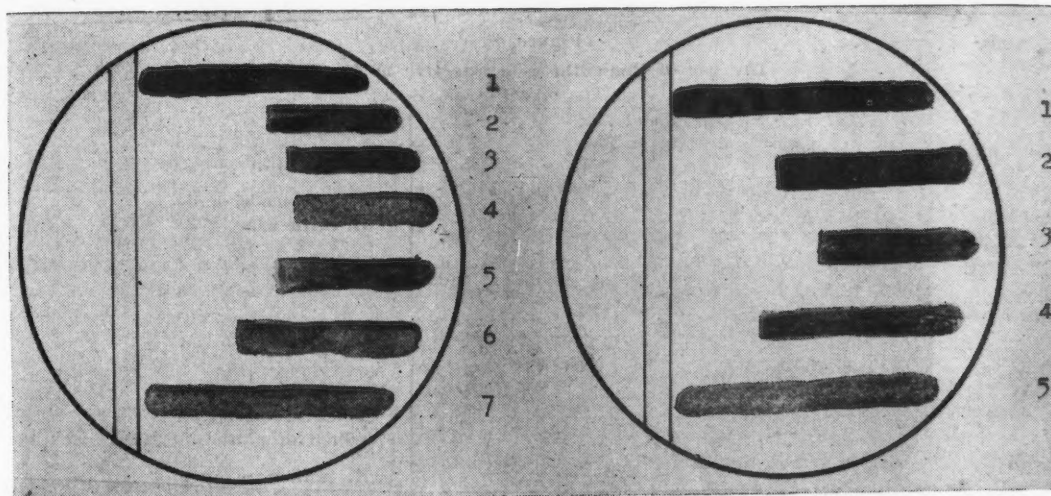
Figure 3.

Bacteriostatic effect of penicillin (I) and of lysozyme (II) on bacteria.

A strip of agar is removed and then replaced by agar containing the bacteriostatic agent. Then different bacteria are streaked across the plate.

Penicillin

Lysozyme



- | | |
|---------------------------|---------------------------|
| 1.— <i>B. coli</i> | 5.— <i>B. diphtheriae</i> |
| 2.— <i>Staphylococcus</i> | 6.— <i>Anthraxis</i> |
| 3.— <i>Streptococcus</i> | 7.— <i>B. influenzae</i> |
| 4.— <i>Gonococcus</i> | |

- | | |
|-----------------------------|---------------------------|
| 1.— <i>B. coli</i> | 4.— <i>B. subtilis</i> |
| 2.— <i>Sarcina</i> | 5.— <i>Staphylococcus</i> |
| 3.— <i>M. lysodeikticus</i> | |

Then the mould was grown on a fluid medium (ordinary bacteriological broth). It grew as a felt on the surface leaving the fluid below quite clear. The fluid was tested at various intervals of growth and it was found that after a week at room temperature it had strong antiseptic properties. The simplest method of test was one which I had previously used for lysozyme. A disc of agar was cut out of a culture plate and the hole thus made was filled with agar containing the culture fluid. Then the surface was planted with a sensitive microbe (staphylococcus) or different microbes were streaked from the edge of the plate to the impregnated agar. When staphylococcus was used there was complete inhibition for a centimetre or more around the culture fluid and when the different microbes were streaked there were some inhibited and some not, just as had been seen with the mould colony in the previous experiment.

When a gutter cut from the agar was filled with culture fluid and different microbes streaked at right angles to it the appearance obtained is very similar to that I had obtained years before with lysozyme using the same technique. This is brought out in Fig. 3. There is, however, a difference and for practical purposes a very important difference. Whereas with lysozyme the microbes most powerfully inhibited were non-pathogenic to man, those most sensitive to peni-

cillin were those which most commonly affect us.

So far I had found that the mould contamination produced a bacteriostatic substance diffusible in agar which was very selective in its action and which affected many pathogenic microbes.

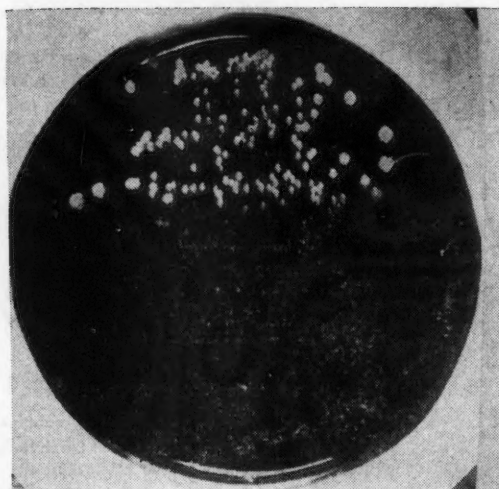
By means of agar diffusion method as described above and by simple serial dilution methods a list of sensitive and insensitive bacteria was made as follows:—

Sensitive

Staphylococcus aureus
Staphylococcus epidermis
Streptococcus (haemolytic)
Streptococcus (viridans)
Pneumococcus
Gonococcus
Meningococcus
M. catarrhalis
Diphtheria group
B. anthracis
Air-borne micrococci
Sarcina

Actinomyces
B. welchii
Vibrio septique
B. oedematis
B. tetani
Spirochaetes

Figure 4
The use of Penicillin as a selective medium



No penicillin
(Staphylococci and
H. influenzae)

Penicillin spread on
surface of plate.
(H. influenzae only)

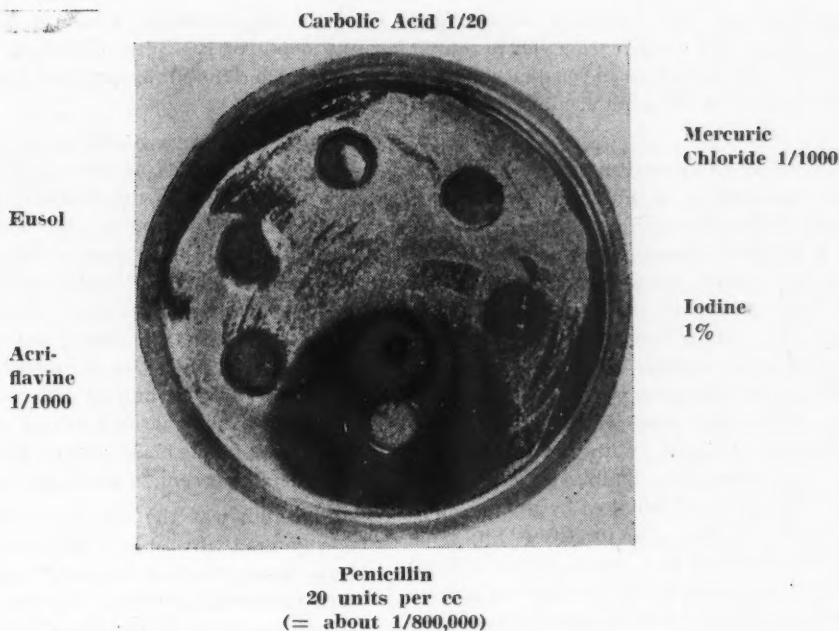


Fig. 5—Comparison of diffusibility of Penicillin and some other antiseptics.
(Discs of blotting paper soaked in antiseptic imbedded in agar plate inoculated with *Staphylococcus*.)

Insensitive

Enterococcus
Non-pathogenic gram-negative cocci found
in the mouth.
B. pyocyaneus
B. proteus
B. friedlander
B. coli
B. typhosus
B. paratyphosus
B. dysenteriae
V. cholerae
Pasteurella

Brucella abortus and *melitensis*
B. tuberculosis

(N.B. Those below the line have been added since my original paper in 1929.)

This immediately suggested the first practical use of penicillin, namely for differential culture. If penicillin is incorporated in the culture medium whether it be plain agar, serum agar, blood agar or boiled agar (or the corresponding fluid medium), the penicillin sensitive microbes are completely inhibited whereas the insensitive mic-

robes grow freely. Thus it was found to greatly facilitate the isolation of penicillin insensitive microbes such as Pfeiffer's *Bacillus* or *B. pertussis*, which are usually found in association with streptococci or pneumococci in the respiratory tract. Indeed it was not necessary to make up special media containing penicillin. A simple method was to inoculate the culture plate with the infected material in the ordinary way and then to spread 5 or 6 drops of the crude penicillin over half the plate. In this way one half of the plate was an ordinary culture and the other half (that to which the penicillin was applied) was highly selective. (Fig. 4.) By this method Maclean and I showed that haemophilic bacilli of the *B. influenza* type were constantly present in the mouth and throat of healthy individuals and that Bordet's whooping cough bacillus could be isolated with greater ease and frequency. It is strongly recommended that this procedure be carried out in clinical bacteriology in all cultures from the respiratory tract. It was also found that by accurately regulating the amount of penicillin in the medium a less sensitive microbe could be grown in pure culture from a mixture with a

more sensitive one. Thus Craddock (1943) added to glucose broth just enough penicillin to inhibit staphylococci and succeeded in constantly obtaining pure cultures of the acne bacillus from acne pustules.

I also used penicillin to demonstrate other bacterial antagonisms in a dramatic fashion. The following is a typical experiment. The mould was grown in a single colony on one side of a culture plate for say 5 days. Then chromogenic bacteria (*Staphylococcus aureus* and *B. violaceus*) were streaked singly and mixed from the edge of the plate to the mould colony. *B. violaceus* being insensitive to penicillin grew right up to the mould. *Staphylococcus* being sensitive was inhibited for a considerable distance. With the mixture the staphylococci completely inhibited the *B. violaceus* until it was itself inhibited by the penicillin when the *B. violaceus* grew profusely up to the mould colony giving in a single streak a distal portion of a golden colour and a proximal portion coloured deep violet. This is especially striking if the culture is made on a paper disc laid on the agar. The coloured growth of the bacteria and of the mould shows up beautifully on the white paper which can be removed, sterilised in formalin vapour and mounted on a card like a photographic print.

We studied the properties of the crude penicillin. We found that it could be sterilised by Seitz filtration without loss of potency. It could be heated momentarily to boiling point without much loss but if it were heated for an hour it was destroyed.

In keeping it gradually deteriorated — some samples much faster than others. In ordinary broth the culture medium became very alkaline and it was found that it did not deteriorate so fast if the pH was adjusted to about 6.8. Our practice was to add phenol red to the filtrate and then sulphuric acid till the red colour just changed to yellow.

It was very diffusible in agar—the first experiments showed that. A simple experiment shows its diffusibility compared with some of the older antiseptics. From an agar plate, discs are cut out with a corkborer. Into the holes thus made discs of filter paper soaked in antiseptic are placed. The holes are then filled up with agar and *Staphylococcus* is planted over the surface. Before the antiseptic can affect the growth

of the *Staphylococci* it has to diffuse through the depth of the agar. Penicillin was the only one which diffused through and inhibited growth. (Fig. 5.)

Then the toxicity of the fluid was tested. Injected into animals, it was no more toxic than the broth on which the mould had been grown. I was more interested in toxic action on human leucocytes. I had previously shown by the slide cell technique that all antiseptics in common use were more toxic to leucocytes than they were to bacteria. If we take phenol as our example, I found that if phenol in a concentration of 1 in 640 were added to human defibrinated blood infected with staphylococci all the cocci grew out whereas the same blood without phenol would kill off some 95 per cent. of the staphylococci. (Fig. 6.)

Penicillin was the first substance I had ever encountered which had a stronger action on bacteria than it had on leucocytes, and it was this fact, more than any other, that led me to suggest that it would be an efficient treatment for infection with sensitive microbes. But before it became a practical therapeutic method it had to be concentrated and stabilised and this we failed to do—we were bacteriologists, not chemists.

Shortly after, however, Raistrick obtained our mould culture and showed that it made penicillin in a simple synthetic medium. He succeeded in partially concentrating it, but he lacked complete bacteriological cooperation so he had to close down the research and there the matter rested until 1938 when Chain and Florey decided to conduct a systematic research on antibody substances.

By that time the whole medical atmosphere on chemotherapy of bacterial infections had changed. In 1929 there was nothing but Salvarsan which had a very limited application. Then the sulphonamides had appeared and Dubos had shown that from a bacillary culture he could obtain a very powerful antibacterial substance.

Florey and Chain studied the literature—fortunately on penicillin there were only about two or three papers—and decided that penicillin was a profitable subject to work on. They obtained my culture and used Raistrick's medium and succeeded in concentrating penicillin about 1000 times and by drying the concentrate they rendered it relatively stable.

The team of workers at Oxford repeated our

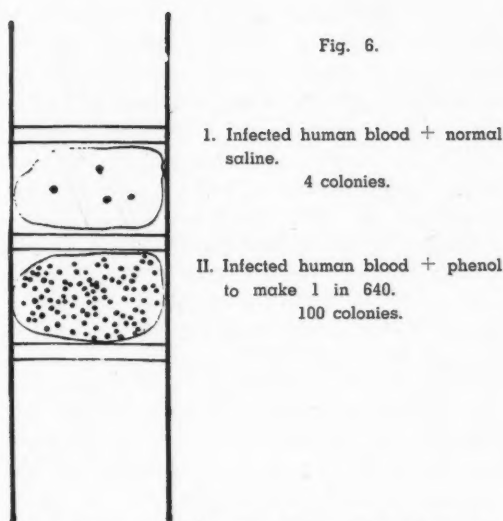


Fig. 6.

I. Infected human blood + normal saline.
4 colonies.

II. Infected human blood + phenol to make 1 in 640.
100 colonies.

Illustrating the greater destructive effect of phenol on leukocytes than on bacteria.

*Test organism = staphylococcus
Inoculum = 100 cocci per cell*

laboratory work and extended slightly our list of sensitive and insensitive microbes. I had shown that the crude material was apparently non-toxic to animals and leucocytes. They showed that the concentrate was likewise non-toxic. Whereas I had said it was bactericidal as well as bacteriostatic, they at first maintained that it was merely bacteriostatic. Its bactericidal properties have since been amply demonstrated. My very first observation on penicillin also showed that it could induce bacteriolysis.

Gardner showed that it had an extraordinary effect on the morphology of the bacterial cell. It seemed to interfere with cell division and sensitive bacteria grown in weak concentrations of penicillin presented extraordinary forms.

Then the Oxford team demonstrated its remarkable curative properties in experimentally infected mice—a few milligrams was enough to cure 100 per cent of mice infected with staphylococcus, streptococcus or vibron septique. Then they tried it on man with some remarkable results.

After that it was a question of production. Florey went to America and passed his information to the authorities there. The pharmaceutical manufacturers there, encouraged by the government, took up large scale production and they have made advances in several directions.

1. Culture medium. They introduced a substance "Corn steep liquor" into the medium and this increased the yield considerably.
2. Method of culture. At first penicillin was made by growing the mould in bottles on a shallow layer of fluid. A method was developed whereby the mould was grown in large tanks well aerated and kept in motion. Industrially this was a great advance.
3. The actual mould culture. At first all the penicillin was made by the original strain of mould which I had isolated in 1928 at St. Mary's Hospital. By various methods mutants were obtained from this culture and an active search was made for better strains. One was discovered on a decaying canteloupe in the Peoria market which in submerged culture gave an increased yield, so that now penicillin is manufactured from more than one strain.

During the Summer I had an opportunity of seeing the largest factories manufacturing penicillin by the tank method and it was interesting to see how a simple laboratory investigation in a London hospital had led by devious paths to a large industry.

Meanwhile the chemists have been busy purifying penicillin, attempting to ascertain its chemical constitution and trying to synthesise it. In the last two respects there is still secrecy, but pure penicillin has been prepared as colourless crystals. It has been discovered that the mould makes more than one penicillin which have been named in England as Penicillin 1, 2, 3 and 4 and in America as F, G, X and K. As medical practitioners we can, however, for the moment neglect these differences.

The Oxford workers when they concentrated penicillin established a unit of potency. This was an arbitrary unit but it corresponded roughly to the amount which, dissolved in 50 cc., would inhibit the growth of staphylococci. This Oxford unit has been established as an International Unit and pure penicillin (2 or G) has a potency of 1666⁶ units per mg. Thus 5000 units of pure penicillin weighs 3 mg. and doubtless in the future the dosage will be calculated in milligrams instead of units.

Penicillin is an organic acid which really forms salts. In common use we have the Sodium and Calcium salts. Both are very soluble in water. The sodium salt is very hygroscopic and is the

less suitable for the preparation of powders or lozenges where a certain amount of exposure to the air is necessary in the dispensing. The Calcium salt is less hygroscopic and, so far as we know, it can be used equally as well as the Sodium salt for injection.

Now that we have penicillin for therapeutic purposes we have to use it intelligently. There are a few very simple rules for its administration which should be followed. These are—

1. It should only be used on an infection by a penicillin sensitive microbe.
2. It should be administered in such a way that the penicillin comes into contact with the infecting microbe.
3. The amount of penicillin administered must be such that the concentration is sufficient to kill the infecting microbe.
4. It must be administered for a sufficient time for the infection to be destroyed.

These may seem childish rules but in practice they are frequently broken. Let us take them in more detail.

RULE 1. *It should only be used in infections by penicillin sensitive microbes.* I have given a list of sensitive and insensitive microbes as tested in vitro and it has been found that the therapeutic results of penicillin correspond exactly to the in vitro tests. There are a number of simple methods of testing the sensitivity of the infecting organisms and this can be done on the primary culture.

The simplest method is to plant out the infective material in the ordinary way and then to apply penicillin of known strength (say 2 units per cc.) to a localised portion of the culture. This is done by means of agar cups or cylinders, filled with penicillin or filter paper discs containing penicillin, and an estimate of the sensitivity of the organisms can then be ascertained.

In the past it has been usual in many cases for the practitioner to treat diseases without actually knowing the nature of the infection. If penicillin treatment forces the practitioner to ascertain what is the infecting microbe it will have done a good service and if a practitioner wants to use penicillin without disappointment this is necessary. Let us take pneumonia. Usually this is due to a penicillin sensitive microbe but it may be an infection by Friedlander's bacillus. By all means let the patient have peni-

cillin at once while the bacterial diagnosis is being made but let the bacterial diagnosis be made and if the patient is infected with an insensitive organism stop the penicillin.

RULE 2. *Penicillin should be administered so that it comes into contact with the microbe.* Although this instruction is very obvious it is frequently disobeyed. There are only two methods of getting penicillin at the infecting microbes. It may be given so that it gets into the blood stream and reaches the microbes through the circulation. This is easy but is expensive in penicillin. The other way, which is only applicable in certain cases, is to administer it so that it reaches the infecting microbes directly without entering the bloodstream. This is very cheap in penicillin but may require much time and patience on the part of the medical attendant.

RULE 3. *Penicillin must be administered in sufficient doses that it reaches the microbes in effective concentration.*

Before systemic treatment can be intelligently carried out the fate of the penicillin which is administered should be known. It is necessary to know how soon the penicillin gets into the blood and how long it remains there in effective concentration. In the blood 90 per cent of the penicillin circulates in the serum so an estimation of the penicillin content of the serum suffices. There is no chemical test for penicillin—it is estimated only by bacteriological methods.

In all the methods of assay of penicillin in blood serum, serial dilutions of the serum are made and these are inoculated with a sensitive organism which grows well in serum and in such a way that the growth is readily manifest. As the supply of serum may be limited micromethods are highly desirable. I first used staphylococcus as the test microbe, as this grows in well defined colonies in serum when incubated in a capillary space such as a slide cell or a capillary tube. This organism is still used by many observers but I now prefer a haemolytic streptococcus using human blood as an indicator. With this combination very good end points are obtained as if the streptococcus grows the blood is haemolysed but if there is enough penicillin in the serum dilutions to stop the streptococcal growth, the blood corpuscles settle to the bottom undissolved. It is impossible to enter into details of the technique here. They can be obtained by reference to our original papers in the Lancet, (1944).

By these methods the concentration of penicillin in the blood has been followed out. If a dose of 15,000 units is administered intravenously, the blood, taken 1 minute after, contains about 3 units per cc. of penicillin. The concentration very rapidly drops and after 10 minutes the serum may contain only about half a unit. Penicillin is excreted rapidly by the kidney and is to be found in high concentration in the urine. The very rapid drop after the first intravenous dose is probably largely due to the penicillin diffusing into the tissues but the fall continues at a slower rate and in 2½ to 3 hours there is no penicillin to be found in the blood. After the same dose injected intramuscularly, penicillin can be found in the blood in 2 minutes and the blood level is at its highest point in 5 or 6 minutes. This is maintained for about 10 minutes and then the curve falls and in 2½ to 3 hours detectable penicillin disappears. After subcutaneous injection the curve is almost the same as with the intramuscular dose except that it may not appear in the blood quite so rapidly. With larger doses the blood content of penicillin rises to a higher level and it can be detected in the blood for a longer period. (Figs. 7, 8, 9.) A dose of 100,000 units will last for about 6 hours but the same amount given in 15,000 doses every three hours will maintain a blood level for some 20 hours so that the small doses often repeated is more economical in penicillin. Carrying this further the most economical way to obtain a constant effective blood level is the continuous drip method, where 60,000 units will maintain a detectable level of penicillin in the blood for 24 hours. This drip may be given intravenously, intramuscularly or subcutaneously. The drawback to the intravenous drip is a tendency of the present impure penicillin to cause

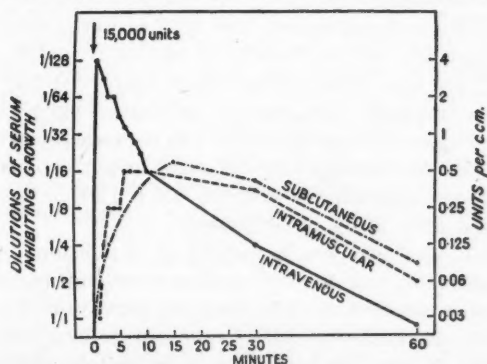


Fig. 7 —Bacteriostatic power of serum following injection of 15,000 units penicillin intravenously, intramuscularly, and subcutaneously.

clotting in the vein after a day or two. With the intramuscular and especially the subcutaneous drip a lesser amount of fluid must be used. This has introduced technical difficulties but I would like to commend to you an apparatus designed by Last (1945). This consists of a small motor which turns a spindle once every hour advancing it 1/16th inch each hour or 1½ inches per day. This spindle presses on the piston of a 20 cc. Record syringe which contains the penicillin solution and which is connected by a narrow rubber tube to the needle. Thus a 24 hour supply of penicillin solution is contained in about 14 cc. of fluid. This fluid is extruded at the rate of 1 drop in 5 or 6 minutes and as absorption even from the subcutaneous tissue is more rapid there is no accumulation of fluid at the site of injection.

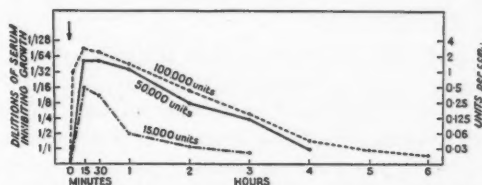


Fig. 8 —Bacteriostatic power of serum following intramuscular injection of 50,000 and 100,000 units of penicillin. Result with 15,000 units included for comparison.

Systemic penicillin may be given by inhalation of a very fine mist of penicillin solution. Many different types of apparatus are on the market which can be adapted for this purpose. When penicillin is inhaled, it readily passes into the blood stream but the absorption is not so rapid as after injection and with the same amount of penicillin detectable blood levels exist for a longer period than when the fluid is injected. It is present also in the sputum in considerable concentration and it seems likely that for many cases, especially bronchitis, the inhalation method will be the method of choice.

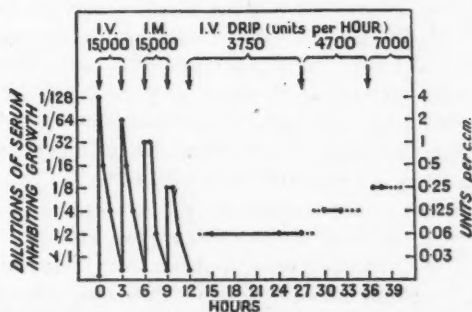


Fig. 9 —Result of intravenous and intramuscular injections and an intravenous drip at various rates on the bacteriostatic power of serum.

Many attempts have been made to administer penicillin satisfactorily by the mouth, since if this could be done it would make the treatment so much easier. The Oxford workers in their earliest papers showed that much of it was destroyed by the acid in the gastric juice but there have been many later publications indicating that therapeutic amounts could be absorbed from the alimentary tract especially if it was given in a buffered solution. We have found that if penicillin was swallowed in gelatin capsules some reached the blood, but if the gelatin had been treated in such a way that its solution was delayed none could be found in the blood. However, no one has yet devised a satisfactory method of oral administration. All the present methods are wasteful and require 4 or 5 times as much penicillin, so until the supply of the drug is ample they are not to be recommended.

Local Administration. Where the infected area is quite superficial penicillin can be applied locally so that it reaches the infecting microbes without entering the blood stream. It may be so applied in the form of solution, cream, powder, snuff, lozenges or lamellae and doubtless many other types of pharmaceutical preparations will appear. This type of treatment is very economical in penicillin but it often requires more time and thought on the part of the medical attendant.

The diffusion of penicillin from the blood into abscesses may be a slow process and the treatment may be hastened by direct injection of penicillin into the abscess and possibly the indurated tissue surrounding it. Penicillin injected into an abscess is not rapidly absorbed and after 24 hours there is generally a considerable amount still present.

Penicillin does not readily pass from the blood into the meningeal cavity, the infected pleural cavity, or into joint cavities but it can be injected directly into these and, just as in the abscess cavity, it is not rapidly absorbed but remains active for 24 hours or more.

Frequently, of course, local treatment is combined with systemic treatment so the infecting microbes are attacked from all sides.

RULE 4. *The treatment must be continued for a sufficient time to eliminate the infection.*

If the treatment is stopped too soon there will be, in many cases, a relapse. This does not always happen, as often the body defenses can deal satisfactorily with the infection if it is curbed

by penicillin. The importance of the continuance of treatment is shown especially in subacute bacterial endocarditis. If large doses of penicillin are given over a period of a few days only the blood is rendered sterile but there is invariably a relapse in about a week. If, however, smaller doses are given and the treatment is continued for 4 weeks or maybe longer, then there is a permanent sterilisation of the blood in some 70 per cent of the patients.

Danger of underdosage.

Penicillin is to all intents and purposes non-toxic so there need be no fear of overdosage. In this it is unique among chemotherapeutic drugs. But there may be a serious danger in underdosage and this danger will be especially manifest if, when the supply becomes plentiful, penicillin can be bought in the shops without a prescription. It is only natural in these circumstances that many people with trifling ailments will treat themselves. It can easily be demonstrated in the laboratory that exposing microbes to insufficient concentrations of penicillin induces them to become resistant to penicillin and the same thing has sometimes been observed in the body. Fortunately it is not too easy to render microbes resistant to penicillin as it is to make them fast to the sulphonamides but the danger exists. I would, therefore, issue a strong plea that anyone treating a patient with penicillin should use adequate doses to destroy the infecting microbes and so avoid the danger of the creation of penicillin fast strains which could be passed on from individual to individual and which might ultimately replace the normal penicillin sensitive strains and nullify the great benefits we now receive from penicillin.

Conclusion.

It may be, of course, that in 10 years the name penicillin will be merely of historical interest. There may be something better discovered from the intensive research on antibiotics which is going on all over the world, or the chemists may alter its formula and produce, under another name, something which has all its advantages and none of its disadvantages.

I have told you something of the history of penicillin and I have suggested certain simple rules for its intelligent use. If these rules are obeyed then some marvelous results will be seen but if they are disobeyed there will be many disappointments.

Faculty Notes

It is with the greatest sadness that the *Quarterly* announces the death of Mrs. Nina I. Roberts, wife of Professor Richard C. Roberts of the Department of Physiological Chemistry. Mrs. Roberts died suddenly on January 24, 1946 in Saint Lukes Hospital. Our sincerest sympathy to you, Dr. Roberts, from all of us here in school.

It was with sorrow that the *Quarterly* learned of the death of Lieutenant Allen H. Ferguson, Jr., son of Dr. and Mrs. Allan H. Ferguson. Lieut. Ferguson was killed in action in the European Theatre of War, April 25, 1945. Dr. Ferguson was an Assistant Professor in the Department of Obstetrics.

The *Quarterly* was also shocked to hear of the untimely death of Marine Private Hale Hunt Dickson, who was killed in an automobile accident in Long Beach, California, November 12. The accident occurred the day after he returned to this country after two years' service in the Pacific. Private Dickson's father is the Registrar of The Chicago Medical School. Our heartfelt sympathy to Mr. and Mrs. Dickson.

Dr. Foa has received recently the following communication (No. 101 of the Pontifical Academy of Science) from its president, Father Agostino Gemelli, O.F.M.:

PONTIFICIA ACADEMIA SCIENTIARUM

Communication N. 101, Città Del Vaticano

The Pontifical Academy of Sciences has undertaken to compile a general report of the scientific research-work accomplished throughout the world from 1939, to the present day. The initiative is in conformity with the august wish of the Holy Father to see international scientific communication restored promptly and on a large scale, thus contributing to ease the strained relations existing between peoples, as well as to enrich the fund of human knowledge by new and useful elements. Moreover, the Academy believes that in so doing it is interpreting that spirit of Christian charity, which embraces also the field of spiritual existence, needed for the most effective results of scientific work, and which has been denied to scientists for so long a time, deprived as they have been of means of mutual communication and knowledge of each other's activity.

The Academy appeals, therefore, to its own members and to such scientists as are qualified to assist, asking them for their precious collaboration in this project, which ought to be carried through in the shortest possible time, if it is to attain the object in view.

The general report will consist of a series of particular reports referring to one or more countries and will treat various branches of science, following a distribution that normally will be determined by the best-known scientific journals or reports as selected by the author. Slight duplication may occur in reports covering similar subjects, but the disadvantage will be unimportant in comparison with the time saved in publication.

Each report will comply with the following rules:

- 1) It should be concerned with publications issued since January 1, 1939, up to the time of this report.
- 2) it should be preceded by a synthetic presentation of the situation of the scientific branch considered in the country or countries to which the study refers, and the problems which at the beginning of the year 1939 were of greatest actuality;
- 3) it should relate the most important results attained during the above mentioned period;
- 4) it should include a bibliography of as many works as possible, properly classified, even if they do not refer to the researches described in the general part of the report, because not concerned with most essential results. However, the length of the bibliography will be subordinated to the author's possibilities and to the bulk of material that has appeared during the time in the country or countries in the report; thus the bibliography will not cause any excessive delay in issuing the report.

* * * *

An appeal is launched to all alumni and members of the faculty of the Chicago Medical School for reprints of their publications or for original articles. Please send all material to Dr. Foa. Arrangements have been made with the Italian Embassy in Washington for shipment of the papers to Italy.

* * * *

The Upjohn Company of Kalamazoo has given a grant of \$3,000 to the Department of Physiology and Pharmacology. The money is to be used to support the work of Doctors Foa and Smith and will be used for equipment and for the establishment of an Upjohn Fellowship in Physiology. Miss Harriet Weinstein will be appointed Upjohn Fellow, after receiving her degree in Biochemistry from the University of Chicago.

Dr. Rudolf Dreikurs, Professor of Psychiatry, has been invited to lecture in South America. He is leaving June 1st for an extended lecture series.

Dr. Dreikurs' new book "The Challenge of Marriage" will be published this summer by Duell Sloan, publishers, New York.

Dr. Piero P. Foa, of the Department of Physiology and Pharmacology is leaving on March 31st for San Paulo, Brazil. He will deliver a series of lectures on the progress of biology and medicine in the United States during the war.

Tuberculosis—

(Continued from page 7)

known. There can be no dispute with the assertion that allergy to tuberculin is an indication of the presence of infection healed or active. The only active immunity demonstrable in tuberculosis appears to be that resulting from healed primary infection. It seems permissible then to assume the tuberculin test to be an indication of the simultaneous presence of this type of resistance. With relation to students of medicine and nursing in particular, it must be borne in mind that these individuals constitute a special risk group. Consequently, in view of the data presented here, the persons in this group entering upon exposure to tuberculosis with a negative tuberculin reaction are running a greater risk than those with a positive reaction.

To prevent tuberculosis among nurses and medical students has been the object of public health officials for many years. Two procedures present themselves: first, the use of a strict contagious technique in the handling of tuberculous patients and organs; second, vaccination with *Bacillus Calmette-Guerin* (BCG). Mariette (31) has ably discussed this problem and comes to the conclusion that contagious technique should be supplemented by vaccination. Dobbie (32) arrives at a similar conclusion. Statistics (33) have been forthcoming from many countries showing, first, that BCG vaccination is harmless and, second, that it is efficacious as a preventative measure. It carries with it the advantage of immunity resulting from a healed lesion as indicated by a positive tuberculin reaction. The efficacy of BCG vaccination in adults has been sparsely studied. Heimbeck (3) reported an incidence of 2.8 per cent in vaccinated nurses as compared with 35 per cent in non-vaccinated cases, but the objections to this work have already been pointed out. If these cases of erythema nodosum are deleted, the corrected figures would be 2.5 per cent in the vaccinated and 17.5 per cent in the non-vaccinated. Sakai (34) reported the vaccination of 73 nurses with BCG with no ill effects but the time interval was not great enough to establish efficacy. Holmgren (35) vaccinated hospital personnel in a Stockholm hospital in whom no tuberculosis occurred as compared to 5 cases among 51 initially nega-

tive members of the hospital personnel who were not vaccinated. In Gothenberg, Sweden, vaccination is compulsory for all student nurses who do not react to tuberculin on entrance to training (36).

Scheel ((23) has followed medical students in Oslo for a period of 10 years. He reports that in 295 initially tuberculin negative students who were vaccinated with BCG, there was a tuberculosis morbidity of 1.95 per cent. In 207 students who were initially negative reactors but were not vaccinated, the incidence of disease was 4.6 per cent. This corresponds to Heimbeck's work reported above. Trosier, Bariety, and Nico (37), since 1937, have vaccinated 33 medical students with BCG in a two-year period. During the same period there were 34 medical students who were not vaccinated and constituted the control group. In the latter there have occurred two cases of tuberculosis, but among the vaccinated, there have been none. Although the time interval has not been great enough in most of the reports concerning nurses and medical students, they do seem to show promise.

SUMMARY

Certain statistical data have been presented which tend to indicate that individuals who show no clinical or X-ray signs of tuberculosis except a primary complex and a positive tuberculin reaction are less likely to become tuberculous than negative reactors under conditions of exposure to tubercle bacilli somewhat more than the ordinary. This view does not seem unreasonable in the light of the well-known Koch Phenomenon. There does not seem to be any reason to suppose that the super-infection immunity possessed by tuberculous experimental animals should not be present in human beings who have a healed tuberculous focus somewhere in the body manifesting itself by reactivity to tuberculin.

Evidence is cited that BCG vaccination is innocuous and offers a means of producing a measure of resistance in tuberculin negative individuals, which enhances their ability to ward off or modify initial infection with virulent tubercle bacilli. It seems advisable on the basis of material presented here that tuberculin negative medical students and nurses, representing a special risk group, should be offered this vaccination on entrance to training.

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Action of Insulin—

(Continued from page 10)

it appears that epinephrine has a direct action upon the phosphate esters of muscle, as Soskin and his collaborators found that the concentration of muscle hexosephosphate rises after the injection of epinephrine in the normal or depancreatized animal, whereas it does not change following the injection of insulin in the adrenalectomized dog. Soskin and his collaborators feel that the contradictory results obtained by previous investigators are due to the counter-regulatory actions of pancreas and adrenals through which excessive insulin evokes a secretion of epinephrine and vice versa. The effect of insulin on another aspect of phosphorylation is being investigated in the laboratory⁴. When thiamine is injected intravenously into a normal, unanesthetized dog, part of it combines rapidly with inorganic phosphate to form cocarboxylase. If sufficiently large doses of thiamine are injected a drop in the concentration of blood inorganic phosphate can be observed. A rise in blood cocarboxylase with a simultaneous drop in inorganic phosphate follows the injection of insulin, especially if the basal concentration of cocarboxylase had been previously increased by daily intramuscular injections of thiamine. Depancreatized dogs have very little cocarboxylase in the blood and its concentration does not rise following the injection of thiamine, unless insulin is administered. It appears from these experiments that insulin catalyzes the phosphorylation of thiamine and, therefore, that it might be necessary for its utilization.

In conclusion it may be stated that insulin probably catalyzes the turnover of phosphate, although this is not necessarily associated with a change in the concentration of the various phosphate fractions of muscle and liver.

* * *

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Confusion—

(Continued from page 14)

open. Every human being who is not accepted as equal within the group in which he lives represents his oppression and revolts against it. However, as long as the social forces in his community do not permit him to throw off his shackles, his resentment and rebellion will be limited to subtle expressions of opposition and any open revolt has no chance of lasting success. Domination of one human being by another always creates an unstable equilibrium; but as long as the domination is backed by the social forces in power, few outward manifestations are permitted to indicate the existing inner antagonisms; everything may look smooth and peaceful on the surface. That was the actual condition under which men and women lived together throughout the ages. This picture changed fundamentally when the suppressed one no longer had to accept his subjugation. Those who held power before became increasingly alarmed; the master had to defend his position against the challenge of his former subordinate who in the new order became a dangerous competitor. On the other hand, those who felt deprived in their human rights, no longer placidly

accepted their inferior position. Their open rebellion made them less cooperative, disturbing peace and order on all fronts where a line existed between those who had power, privileges and rights and those to whom they were denied. That is as true for the relationships between men and women as it is for the equilibrium between management and labor, rich and poor, white and colored, majority and minority, between adults and children. On all these frontiers, open hostilities broke out. The competitive spirit was not limited to the struggle between dominant and dominated groups; it penetrated each group in itself as every individual strove to get ahead of his fellowman with whom he was united against their common opponents. It even penetrated the family group, setting father against mother, parents against children, and brother against brother. The result is the complete disintegration of our society, where each individual stands and looks out for himself and regards his fellowman as his enemy.

The sexual and marital problems of our time reflect the existing structure of our society. Men and women are more suspicious of each other, than ever before. And woman is set against woman, man against man, in the strife to gain superiority, prestige and power. They all exhibit the spirit of defensiveness against threatened subjugation and imposition. They use sex and love less for the purpose of gaining happiness and harmony (of which they despair anyhow), than as a tool for power and defense. They either fall in love with an unsuitable partner whom they can blame for all troubles or they avoid falling in love altogether. Jealousy becomes a symbol of "love." Emotions become unreliable guides as the individuals refuse to accept each other fully. Increased frigidity and impotence, and the whole host of perversions express the unwillingness to participate with a member of the opposite sex. Exaggerated sexual interest and a false ideal of romantic love as demonstrations of exaggerated overt desire veil only thinly the inner defensiveness. A strong motivation for the behavior of men and women in regard to sex, love and marriage is the so-called "masculine protest" (Alfred Adler). Women no longer accept their position of a secondary role in society; they are afraid of masculine domination but are not yet sure of their own ability to gain equality. And men, on the other hand, lose their confidence in main-

taining their superior positions; while the ideal of a strong man still persists, many men today doubt their ability to be a "real" man in a time when education, social and economic possibilities for women make it impossible for men to excel as they did in the past.

The general attitude of fear and suspicion is intensified through the lack of the traditional and moral forces which had kept women "in their place". Previously, every man was sure of his position, because conventions and customs made man the unchallenged master in the family and in society. Today, each individual has to stand for himself and find his own place not only within society, but in regard to the opposite sex. Complete chaos characterizes the present equilibrium between the sexes. There are no general standards for the social position of women. Each country is in a different phase of development, some granting women more of the rights which were previously in the exclusive possession of men, some less. And within the same country, national, racial and religious groups, even cultural and economic units differ in their moral and social standards for women. Some couples are united in a typical patriarchal relationship where the husband has all the rights and the wife none; other couples show the reverse, characteristic for matriarchal relationships. And in between the two extremes lies a great variety of all types of equilibrium possible. The sense of insecurity is tremendous. The dynamic freedom *given to each individual* to seek his own position, at the same time deprives him of a sense of certainty about his "rights" and his obligations. As moral values rapidly change, parents get out of step with the conventions governing the group to which their children belong. Children growing up without guidance which they need, become even more confused. Seeking pleasure and prestige, they are not able to evaluate sex properly. They either become afraid of it or abuse it.

The picture does not look bright. Many who cannot see beyond the immediate problems despair in the ability of man to act conscientiously and to live harmoniously with each other. Despite the great confusion and the bitter struggle on all frontiers of human competition, no pessimism is justified. We must only keep in mind that the complete anarchy which seems to affect all order and human relationships today is the result of a definite *progress* which mankind has made during

the last century: the progress toward the establishment of human equality. Peace and harmony cannot be restored until such equality has been actually established. Until then the struggle between those who still hold the power and those who want to share it may become even more bitter and more vicious. But there is no way back, unless we destroy our whole culture. Even that would mean no way back, as we never would be able to return to the status quo, let us say, of one hundred years ago. Progress or destruction are the only alternatives; and although utter destruction of the whole of mankind appears possible today, the natural desire of man to live may be the force which will overcome all the obstacles to progress. The solution of the sexual problem is intrinsically linked with the solution of all our social, political and economic problems. It is impossible to establish true equality and the fellowship of man in one sphere alone. Mutual distrust and prejudice must be overcome in *every* form to enable men and women to live harmoniously together and to use sex as a tool of unification. Once such a stable equilibrium, based on full equality, on mutual respect, has been accomplished, it will become apparent that Sex is no obstacle to social peace and harmony, but, on the contrary—as Love—is one of the most constructive motivations for cooperation.

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Aphorism 47

Pains and fevers occur rather at the formation of pus than when it is already formed.

. . . . a sharp nose, hollow eyes, collapsed temples; the ears cold, contracted, and their lobes turned out; the skin about the forehead being rough, distended, and parched; the color of the whole face being green, black, livid, or lead-colored.—The Hippocratic Facies, from Hippocrates, The Book of Prognostics.

The physician must be able to tell the antecedents, know the present, and foretell the future—must meditate these things, and have two special objects in view with regard to diseases, namely, TO DO GOOD OR DO NO HARM. The art consists in three things: The disease, the patient, and the physician. The physician is the servant of the art, and the patient must combat the disease along with the physician.—Hippocrates, First Book of the Epidemics.

* * *

Military physicians under Caesar were underpaid. They received only about \$50 and board per annum. Under Domitian (reigned 81-96 A. D.) they received \$66, and under the liberal Septimius Severus, about \$110.—Arch. Ophth.

Social Notes

Happy birthday to:

Miss Carolyn Brown, daughter of Joe Brown, born April 17, 1943.

Master Robert J. Dillon, son of Dr. Milton Dillon, ('43), born on April 6, 1944.

Master John C. Gornstein, son of Dr. H. Gornstein ('44), born on March 30, 1944.

* * * * *

The Junior Class wishes to announce that their Prom will be held April 13th at the Belden-Stratford Hotel. They would like to see as many couples as possible present.

* * * * *

Congratulations to Dr. and Mrs. S. A. Garroway, '43, of 648 Eastern Parkway, Brooklyn, N. Y., on the birth of their son Neil Warren, on December 26, 1945.

* * * * *

William Jeffrey Wolf was born to Dr. and Mrs. Marvin B. Wolf, '44, on February 13, 1946. The little bundle was dropped in Chicago. Congratulations, Marvin.

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Separated—

(Continued from page 19)

Mayer, Edward J.	CMS 1931
McNamara, J. C.	CMS 1942
Miller, Robert E.	CMS 1938
Moskal, Frank J.	CMS 1930
Motier, Jean H.	CMS 1934
Nierenberg, Paul S.	CMS 1937
Paolozzi, Hannibal	CMS 1938
Parrott, Elmer L.	CMS 1938
Pava, Charles	CMS 1932
Reynolds, Edwin C.	CMS 1929
Shear, Henry R.	CMS 1940
Simonelli, Mario	CMS 1934
Sloan, Howard	CMS 1942
Sonenschein, Benjamin	CMS 1933
Sowden, Paul R.	CMS 1931
Steiniche, Aage	CMS 1924
Tanenbaum, Lewis	CMS 1938
Wendorf, Albert	CMS 1939
Yacullo, William A.	CMS 1938
Zurawski, Walter F.	CMS 1934
Metro, Michael L.	CMS 1930
Tobey, Albro C.	CMS 1940

Letters to the Editor

Feb. 19, 1946

To the Editor of the *Quarterly*:

Thank you for your very nice letter. I look forward to each issue of the *Quarterly* and enjoy reading it very much.

As for what I am doing now, I am practicing in El Monte, California, and I own the Stanley Hospital there, an institution of twelve beds. My practice is very large and I employ three doctors who are my assistants. I expect to expand the present hospital with a new modern hospital building with modern equipment and of thirty bed capacity.

Again I want to thank you for your very nice work.

Sincerely yours,

Joseph A. Marlo, M.D.

* * * *

March 14, 1946

To the Editor of the *Quarterly*:

Just got a copy of the *Quarterly* and thanks a million—the alumnae notes were especially interesting to me.

My own Navy career has been rather saltless; but things appear to be popping right now. Started off in a combat training course, used every type of firearm, had gas attack, swimming in water with fire and oil, unexploded ordnance, field drill, obstacle courses, etc. Came V-J Day and got transferred to Oak Knoll Naval Hospital—a 6000-bed institution. This place was top-notch, certified by all Boards. I got several months of training in all phases of Gastro-enterology. Did gastroscopy and sigmoidoscopy, peritonoscopy, etc. Saw practically every type of G.I. case and what was most striking was to see advanced Ca of the stomach in 20-year-old men. We were assigned to clear up the bacillary epidemic (Shiga), which hit the 3rd Fleet on its way back. Sulfadiazine cleared up 95% of the men and the rest were then switched to sulfaguanidine with fine results. Especially interesting was a group of our own marines who had been captured in '41 on Wake, Midway, etc. Several hundred were included. We all see the sob-sister stories about patriotism; but I saw marines big and tough stand on the Quarter-deck for 15 minutes with tears in their eyes looking

at Old Glory. This group of men had menageries of intestinal parasites and all were clinical avitaminoses in advanced stages. We had several who were clinical beri-beri—both wet and dry, who went on to have cirrhosis proven by lab. test, peritoneoscopy and liver biopsy. These are perfect controls for avitaminotic cirrhosis, since they certainly got no alcohol from the Japs. At present am at the District Medical office, carrying on a large office practice on Naval personnel and their dependents. Could go on and tell many more interesting stories, especially of the tropical diseases with which we had so little contact back in Chicago. But all things have to stop.

Thanks again and good luck to all of you. Give my best wishes to Dr. Sheinin and others of our mutual acquaintances.

Fraternally yours,

Joseph Turbin, Class of '44

Office of Commandant

Twelfth Naval District

San Francisco 2, California

* * * *

March 30, 1946

Dear Editor:

I always enjoy the *Quarterly* and the activities of the boys.

When I finished after two years at Dunning and three years at the Cook County Psychopathic—11 p.m. to 7 a.m.—I was about dilapidated. It took me about two years to recover from the ordeal.

Now we are in a position to offer an opportunity for one doctor each year to get his breath and a perspective of his future; also a little remuneration that might tide him through his first year of starvation.

I will be in Chicago for the meeting of the convention in May. If there is one of the boys who is interested, I shall be glad to meet with him and talk over the details. If there is more than one perhaps it can be arranged so that we can all meet together.

Yours fraternally,

E. W. Burroughs

Burroughs-Stanelle Medical Center

Shawneetown, Illinois

Abstracts

THE CLINICAL TOXICITY OF THIOURACIL.

Survey of 5,745 cases. Drs. Winkle, Hardy, Hazel, Hines, Newcomer, Sharp and Sisk. A.M.A. Journal, Vol. 130, No. 6, Feb. 9, 1946, pp. 343-7.

Clinical response to thiouracil may not be seen for several weeks, especially if iodine has been previously administered; however, thiouracil is effective and is used in the treatment of thyrotoxicosis and possibly thyroiditis. It should not be used in any conditions which are not associated with hyperthyroidism.

There have been four principle toxic reactions seen. These consist of a granulocytopenia in 2.5% of the patients, a leukopenia in 4.4%, drug fever in 2.7%, and a dermatitis in 3.3%. Less common reactions seen were: G. I. symptoms, parotitis, joint pains, purpura, jaundice, diarrhea, thyroiditis, and secondary anemia. However, these conditions may or may not be related to the administration of the drug because of their low incidence in a large group of patients.

Presence of a granulocytopenia appears to be the most serious complication. (It was diagnosed if the white count was below 4,000, granulocytes diminished and there occurred a sudden onset of such acute symptoms as fever, sore throat, prostration, and malaise.) A mortality rate of 14% was seen resulting directly from this complication, with a mortality rate of 0.4% for the entire series.

The conclusions concerning the relative safety of thiouracil indicate that the incidence of toxic reactions to the drug is less than complications resulting from other methods of treating hyperthyroidism.

S. R.

* * * * *

PROGRESS IN CANCER RESEARCH. John J.

Morton, M.D. Connecticut State Medical Journal, March 1945. Vol. 1X, No. 3, pp. 167-175.

DESPITE the war, definite progress toward solving the problems of cancer has been made without interruption. The advances are best grouped as given below:

New Animal Experimental Material: Great strides have been made in induction of cancer

by the use of carcinogenic coal tar derivatives on frogs, dogs, and monkeys. The latter also have been seen to develop spontaneous tongue cancer with of course no question here of the debatable roles of hot foods, rough dental plates, tobacco, etc. which are considered of importance by some in human malignancy.

Tissue Changes in Carcinogenesis: A most significant change here has been noted in the production of skin carcinoma in mice by a single application of methylcholanthrene. Such work may necessitate changing our whole conception of carcinogenesis as dependent on prolonged repeated trauma. Confirmation of this has come from development of malignancy in mice subjected to but a single dose of X-ray. Benzpyrene was noted to be changed quickly upon application to skin giving rise to a blue fluorescent derivative, thus this changed substance may be the significant inciting factor rather than the original.

Tissue Cultures: Production of malignancies in vitro has been an excellent advance in our studies of the true mechanism of malignant growth. Very significantly, study of Hodgkin's disease in tissue culture seems to rule out bacteria as the pathogenic agent; in several hundred cultures no specific bacterial contamination was observed.

Tissue Enzymes: Enzyme systems undergo manifest changes in the transition from normal to neoplastic tissues; some vanish while others appear to remain the same or increase, such studies are extremely complex, however, even for an individual type of tumor. Extremely interesting findings such as the phenomenal proportion of potassium in hepatomata lead to great speculative activity. Alkaline phosphatase, so characteristically increased in bone tumors as osteogenic sarcoma, is practically absent in intestinal adenocarcinoma.

Hormonal Studies: Pituitary, thyroid, and lutein hormones have never been found to cause or control any cancer. Estrogens repeatedly have produced mammary, uterine, testicular, and other tumors in some species when exposure is prolonged. The transmission of a carcinogenic factor for mouse mammary carcinoma has been proved to be effected via the mother's milk. The active principle is believed to be a colloid of high molecular weight—possibly a virus. Intrauterine environmental factors are also important in development of carcinomatous strains of mice. In

one strain, gonadectomized at 2 days of age, 100% developed carcinoma of the adrenal cortex by the age of 1 year. It is significant that in these conditions, no carcinogens of any kind were added in the experiments, showing the agents responsible to be entirely endogenous. Repeated administration of diethylstilbestrol in treatment of advanced prostate carcinoma has shown much improvement in humans. Serum acid phosphatase is found increased when the human prostate carcinoma has undergone widespread metastases. Caution is necessary in transferring animal results for purposes of making conclusions about human cancer, but tendencies are definitely indicated for consideration.

Light Effects: Rat and mice tumors have been produced by ultra-violet radiation and definite wave length ranges have been found necessary. About 94% of these are sarcomas, believed by some to be due to the thinness of the skin in

these animals, allowing penetration beneath the epidermis, while in man radiation-induced tumors are epithelial. The carcinomatous growth, once initiated, proceeds without further irradiation.

Heterotransplantations: Transplantation of malignant tumors into the anterior chamber of rabbit's eyes and other regions has led to much research in this field. Adult normal tissues cannot be transplanted to alien species, while embryonic tissue can. Benign tumors and precancerous lesions cannot as yet be transplanted at all. It has been concluded from this work that the acquisition of malignancy was a series of progressive changes of hyperplasia, anaplasia, local invasiveness, and complete autonomy. Since the only tissues transferable to a foreign species were normal embryonic and tumor tissues which had attained complete autonomy, one change in cancerous development of a cell is believed to be loss of species identity.

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Viruses: Mouse sarcoma virus passage in avians of the same and different species by intravenous inoculation has produced 2 different types of tumors. Mouse mammary tissue was grown in chick embryo yolk sac culture, and the yolk from this was diluted and passed through an N-sized Berkefeld filter, producing transplantable malignant tumors when injected into this strain of mice. This latter work is of especial significance and awaits confirmation by further studies.

Studies of Cancer in the Human Subject: Carcinogenic substances have definitely been extracted from various tissues of humans who have died of cancer. No evidence of conversion of normal cells to cancerous was found in observations of an epithelioma; the tumor cells behaving as an isolated colony of mutation spreading into adjacent tissues. Syphilitic women have been found to develop more extensive, less favorable, and earlier incidence of carcinoma of the cervix. Undescended testicles show greater tendency to become malignant than scrotal ones. Radioactive substances with predilection for special organs are now used in cancer therapy for these organs. The greatest hope as yet available today is in

further development of prevention clinics, with wider dissemination of cancer education so that earlier recognition and treatment can be effected.

S. I.

* * * * *

No matter if the man has brains
Enough for a degree,
He still appreciates the things
That interest you and me.
Though he may be a Bachelor
Of Arts . . . then certainly
He knows there's more to subtle curves
Than what the eyes can see—
Or maybe he's a Master
Of the Sciences so great,
Then surely he knows chemicals
Aren't all that he can make.
Do wondrous tricks and treats
That roguishly defy
Him to deny he's anything
But an ordinary guy.
So it really doesn't matter
If your friends are Ph.D.'s;
Or if you travel in a set
Of rugged B.V.D.'s—
You've still got eyes to see with
And a heart you shouldn't hide,
Relax and look . . . and brother,
Let your conscience be your guide!

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Asses hoof1 part

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* * * * *

Layman's Misunderstanding

Mr. Jones: "What did you say my boy has?"

Doctor: "He's got a condition known as megacolon."

Mr. Jones: "What is that?"

Doctor: "It is a stretching of the large intestine and he'll have to be operated on!"

Mr. Jones: "No operation."

Doctor: "Either I do an operation or a post-mortem."

Mr. Jones: "Now you're talking. When can you do it?"

* * * * *

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—New England J. Med.

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